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BRAIN.

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OBSERVATIONS ON REFERRED PAIN.

BY CHARLES BOLTON.

The observations described in this communication were made with the object of affording evidence that pain and tenderness in patients with gastric and duodenal ulcer is of the visceral referred type, quite apart from the question as to whether splanchnic pain occurs in addition.

Referred pain does not occupy the important position in clinical medicine to which it is entitled, and the theory of the mechanism of its production as laid down by its originators, more especially Mackenzie, has recently been called into question. The older clinical observers recognized it; for Hilton [1], of Guy's Hospital (1863), believed that morbid conditions of the internal viscera were associated with pain situated on the surface of the body; and Martyn [2], of Bristol (1864), considered that the impression of distress in the heart was received through nerves entering the grey posterior columns of the spinal cord and that the central impression was irradiated and referred by the mind to the sensitive skin. Ross [3] (1888) clearly distinguished this referred, or somatic, pain from splanchnic pain conveyed by afferent sympathetic nerves from the organ, which is the origin of the disturbance. But Mackenzie [4] (1892) gave the first objective evidence in favour of this theory, by drawing attention to associated tender areas in the body wall, cutaneous hyperæsthesia and increased reflex muscular irritability. His most important and decisive observation as regards the abdomen was that by which he proved that the tender areas in patients with gastric ulcers occurred in different positions from that of the ulcers. The point of maximum pain corresponded with this tender area. The pain and tenderness were definitely fixed in position, usually in the central line,

whilst the ulcer was found at an operation or post mortem in different positions lateral to this.

It is unnecessary for my purpose to refer to other work on the subject, except that of Morley [5] (1931). Morley claims that Mackenzie's observations are untrue, and that the position of the tender area corresponds with that of the ulcer. His method was as follows: He first marked out on a chart the point of tenderness in different positions of the patient, and found that this tender point shifted with these changes of position. He then administered a barium meal and again marked the tender point by a metal ring on the skin in both the upright and supine positions. Films were exposed in these positions, and on developing them the ring was always found to coincide with, or be very near to, the ulcer; the ulcer moved upwards when the patient lay down and the tenderness moved upwards in correspondence with it. He, therefore, claims that the area of deep tenderness is accurately localized over the ulcer and moves with it, and that this proves "that the tenderness is not produced by a 'reflex' or radiation through the afferent splanchnic fibres, since that hypothetical process could only give rise to a fixed and immobile tenderness, the position of which would be determined, not by the position of the ulcer in relation to the abdominal wall, but by the distribution of those sensory nerves in the abdominal wall which entered the same segment of the cord as received the afferent autonomic nerves from the ulcer." He made observations on other viscera also and concludes that: "referred pain only arises from irritation of nerves which are sensitive to those stimuli which produce pain when applied to the surface of the body." The tenderness over the ulcer is, according to him, felt in the overlying skin and subcutaneous tissue as a reflex in response to stimulation of the parietal peritoneum in contact with the ulcer.

Clearly this new series of observations and the deductions drawn from them call for careful examination, because the physician, who is accustomed to deal with large numbers of cases of gastric pain, can hardly fail to be impressed with the accuracy of Mackenzie's observations, and with the utility of referred pain in clinical diagnosis. Since it has become possible to localize the majority of gastric and duodenal ulcers with the X-rays, and to palpate them during the screen examination, referred pain has unfortunately been heard less of than before. Radiologists are universally agreed that on thus palpating the stomach the ulcer itself may be demonstrated to be tender. It is not within the purview of this communication to discuss the nature of this tenderness

and its relation to splanchnic pain. It is, however, important to draw attention to the method by which it is elicited, which is quite different from the light palpation of the clinician. In order to palpate the ulcer, the radiographer presses the anterior abdominal wall against it, and squeezes it forcibly against the posterior wall of the abdomen; and in doing this he employs considerable pressure. The clinician, on the contrary, in testing the abdominal wall for tenderness palpates it lightly against the elastic resistance of the abdominal contents, having first ascertained whether cutaneous hyperæsthesia or subcutaneous tenderness are present or not.

In the Croonian Lectures (1928) I described the analysis of one thousand cases of gastric pain [6]. 715 of these exhibited pain in single areas, of which 533 were present in the sterno-umbilical region, 452 being situated in the mid-line and 81 at the costal margins. The pain is commonly accompanied by tenderness, which occurs in precisely

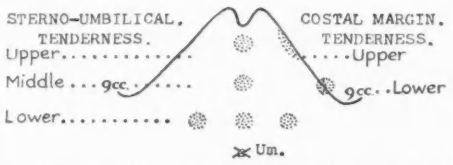

FIG. 1.—To show the areas of pain and tenderness in gastric and duodenal ulcers. Um., the position of the umbilicus. The areas of tenderness in the costal margins are shown in the left side only.

the same area as is painful and corresponds with certain positions on the posterior surface of the body behind. The tender areas, which are constant in position, are most obvious when the pain is at its maximum and they generally outlast the pain. They are present between the individual attacks of recurring pain, finally disappearing more or less slowly when a pain period is ended. A tender point may thus be present without pain; or be present in a different situation than the pain experienced at the same time; or pain may never have been present at the tender spot. Occasionally the painful spot does not become tender. Cutaneous hyper-æsthesia and subcutaneous tenderness are commonly absent; they appear to indicate a higher degree of sensitiveness of the central nervous system than does tenderness of the deeper structures of the abdominal wall. They are particularly liable to occur when the tenderness is diffused beyond the points described, and has affected the whole of one or both sides of the sterno-umbilical

region. Fig. 1 shows the distribution of the tender points in these cases of gastric disease. Most of the points occurred in the central line between the ensiform cartilage and the umbilicus. On this line there are three areas, each about the size of a shilling (2·5 cm.) or larger, namely: (1) At the centre where the transpyloric line joining the right and left 9th costal cartilage cuts it; (2) above this point, just below the ensiform cartilage; and (3) below it near the umbilicus. These three points correspond with the 7th, 8th and 9th thoracic segments, which probably overlap: Head [7], Foerster [8]. There are three further points situated in these segments lateral to the central points just described, namely: (1) in the 9th thoracic segment a few centimetres to the left or right of the central line; (2) in the 8th segment at the costal margin over the right and left 9th costal cartilages, more commonly on the right; (3) in the 7th thoracic segment at the upper portion of the left costal margin, rarely on the right side. The whole central line, or the whole of one or other, or of both costal margins, may be tender; and the tenderness may diffuse over one or other half of the sterno-umbilical region. It will be seen that this description differs from that of Mackenzie in that it includes the lower sterno-umbilical region and the costal margins.

The first and most important objective in the present investigation was to determine definitely the relation of the positions of these tender areas to the positions of the ulcers as seen by the X-rays. The series investigated comprised twenty-five cases of gastric ulcer, thirteen cases of duodenal ulcer, and thirteen cases of painful gastric neurosis. All the cases had been X-rayed and the gastric and duodenal ulcers displayed on the films; all the ulcers were said to be tender to deep pressure. In the cases of neurosis the stomach was proved to be normal by the X-rays and was free from tenderness.

Method of Investigation.

The tender areas were first determined by light palpation, and marked on the surface of the skin in the upright and supine positions; in every case these two positions were exactly the same. A glass screen, which was specially made for this purpose, was then placed on the front of the body and the outline of the costal margin, the position of the umbilicus and the tender areas were marked on it with a coloured pencil. Radiograms were then taken of the stomach in the supine and erect positions immediately after giving a barium meal, so that the stomach was full; the umbilicus was marked with a piece of metal.

The ulcer, which was found to be tender on screening, was shown in each position of the patient in relation to the mid-line and the umbilicus. The X-ray films were then placed under the glass screen, so that the shadow of the umbilicus on the film and the central line of the spine corresponded with the same positions which had been marked on the glass screen, and the positions in which the ulcer was seen were then marked on the glass screen. The distances of the ulcer from the mid-line, and above or below the umbilicus in the supine and erect positions, were measured in centimetres. By determining the length of the sterno-umbilical and transpyloric lines it was quite a simple matter to draw an accurate diagram, reduced to one-third of the normal size, showing the costal margin, umbilicus and positions of the ulcer, together with the tender areas on the skin. When the glass screen was not available, these measurements were obtained from the abdomen of the patient and the measurements of the positions of the ulcer from the X-ray films. The diagram reduced in size to one-third was then drawn. Either method gives the required result, but with the glass screen the exact shape of the costal margin was more certainly determined. In the supine position the ulcer sometimes disappeared under the costal margin, so that the radiologist could not palpate it to say whether it was tender or not.

Results of Observations.

The exact positions of the ulcers and the tender points in the abdominal wall are given in Tables I, II, III and IV; and specimen diagrams of the cases are shown in figs. 2 to 9.

Gastric Ulcer.

I.—*Small Curvature. Twenty-three Cases* (*Table* I).

Tender areas.—As determined by light palpation the tender areas in all cases except two (22 and 23) were situated in the central sterno-umbilical line. In each case the area involved was about the size of a shilling (2·5 cm.) or a little larger. In nine of the twenty-three cases the tender point was situated in the centre of the sterno-umbilical line; in five it was above the centre near the ensiform; and in two it was below the centre near the umbilicus. In one case (21) all three areas were affected, the whole of the sterno-umbilical line being tender and the tenderness diffused outwards towards the left costal margin; in this case alone were subcutaneous tenderness and cutaneous hyperæsthesia present. In two cases (14 and 18) the middle and lower areas were

combined. In one case the tender point was 3·5 cm. to the left of the lower part of the mid-line; in two it was at the right and in one at the left costal margin. The tender areas on the right side were situated at the 9th costal cartilage, one being associated with a tender area in the upper part of the sterno-umbilical line and the other with tenderness in the middle part. All these points were constant in position, whether the patient stood erect or lay supine. The tenderness might be relieved or increased by contraction of the recti. In the erect position the abdomen may bulge out and increase the length of the sterno-umbilical line, but the tender point in such cases always occupies the same relative position in the line by measurement. These areas correspond exactly with those in fig. 1.

TABLE I.—POSITIONS AS DETERMINED BY X-RAYS OF TWENTY-THREE SMALL CURVATURE GASTRIC ULCERS, AND OF THE TENDER AREAS ON THE SURFACE OF THE ABDOMEN.

No.	Name	Measurements of centre of ulcer to left of midline in cm.		Vertical measurements of centre of ulcer above umbilicus in cm.		Shift upwards in cm.	Tender areas on the surface of the abdomen in the erect and supine positions
		Erect	Supine	Erect	Supine		
1	R. T.	4·5	5	0	8	8	Central line—middle
2	A. W.	1	4	4 (below)	2	6	,, upper
3	S. A.	5·5	6·5	4	8	4	,, middle
4	A. M.	3	3	1	6	5	,, upper
5	C. G.	3·5	1	1	6	5	,, ,,
6	E. S.	3·5	4·5	3·5	7	3·5	,, middle
7	H. F.	2·5	3·5	7·5	12·5	5	,, ,,
8	W. D.	5	7·4	0	7·4	7·4	,, ,,
9	E. D.	3	7	6·5	9·75	3·25	,, lower
10	J. H.	4·5	4·5	8	14	6	,, ,,
11	W. J.	4·5	0	3	6	3	,, middle
12	E. du B.	3·5	4	3	14	11	,, ,,
13	T. H. G.	4·5	6·5	5	10	5	,, upper
14	P. C. M.	6·5	5·5	5	8	3	,, middle and lower
15	L. G.	4	4·5	7	11	4	,, upper
16	F. B.	4	2	1·5	4	2·5	,, middle
17	T. M.	7	5·5	3	7	4	,, ,,
18	F. G.	6	5	0	3	3	,, middle and lower
19	H. H.	4·5	6	8	10	2	,, upper and right costal margin 9th c.c.
20	G. M.	4·5	5·5	3	6	3	Central line—middle and 9th right c.c.
21	G. W.	1	3	4·5	4·5	0	Central line—whole and diffusing to left costal margin
22	S. S.	3	4	4·5	8	3·5	Left costal margin upper part
23	A. M.	4	4	3·5	8	4·5	3·5 cm. left of lower part of central line

Position of the Ulcer. Patient Standing.

Horizontal position.—In all twenty-three cases the ulcer was situated to the left of the mid-line, the lateral limits from this position being 1 cm. to 7 cm., and the average 4 cm.

Vertical position.—Three ulcers were level with the umbilicus and one was 4 cm. below it. Nineteen were situated from 1 cm. to 8 cm. above the umbilicus, the average being 4·3 cm.

Patient Supine.

Horizontal position.—One ulcer was situated in the central line. Twenty-two were to the left of this line, the limits being from 1 cm. to 7·4 cm., with an average of 4·6 cm.

Vertical position.—In twenty-two cases the ulcer occupied a higher position than when the patient was standing. The levels varied from 2 cm. to 14 cm. above the umbilicus. One ulcer maintained its vertical position but shifted outwards to the left by 2 cm. In every case except one, therefore, the ulcer shifted upwards when the patient assumed the supine position. The degree of upward shift varied from 2 cm. to 11 cm., the average being 4·7 cm. In fourteen cases the shift was upwards and outwards; in six upwards and inwards, reaching the mid-line in one; in three directly upwards.

In twenty-one cases, therefore, the tender points were situated in quite different positions from those occupied by the ulcer in both the erect and supine positions. These tender points remained in the same position whatever the position of the patient, whereas, in contrast, the ulcers moved upwards in the recumbent position.

These results could not be completely demonstrated in the two remaining cases. For in one (21) the tenderness, which was present from ensiform to umbilicus, extended diffusely leftwards to the costal margin and covered the ulcer in both standing and lying positions; the maximum tender point still, however, remained in the centre of the sterno-umbilical line although the ulcer shifted outwards in the supine position to a point 2 cm. to the left of this point of maximum tenderness. In the other case (11) the ulcer in the erect position was well outside the region of the tender point, but in the recumbent position it moved inwards to the middle line under the tender point which had remained stationary (figs. 2, 3, 4, 5, 6).

II.—*Pyloric Vestibule. Two Cases* (*Table* II).

In each case tenderness was said to be present by the radiographer at the cap and pylorus, and a pyloric ulcer was diagnosed.

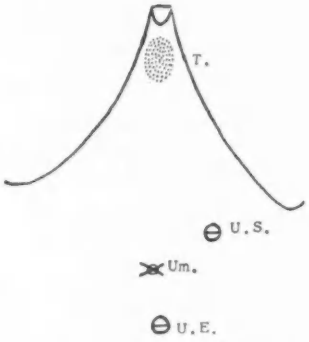

FIG. 2.—Case 2. In this and all the subsequent figures—T., the position of tenderness; U.S., the position of the ulcer when the patient was in the supine position; U.E., position of the ulcer when the patient was standing erect; Um., the umbilicus.

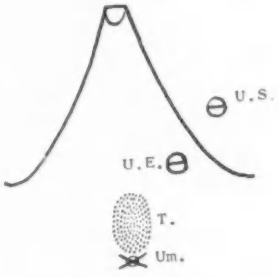

FIG. 3.—Case 9.

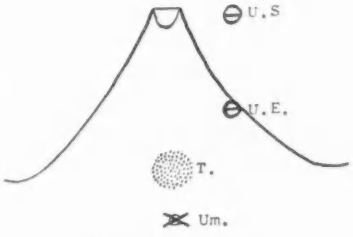

FIG. 4.—Case 10.

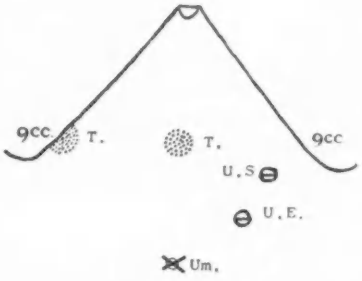

FIG. 5.—Case 20.

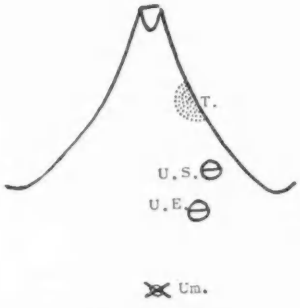

FIG. 6.—Case 22.

One case was inconclusive as far as our present purpose is concerned. There were two tender points of maximum intensity, one at the 9th right costal cartilage and another in the middle of the sterno-umbilical line, but diffuse tenderness extended between this line and the right costal surface, and there were subcutaneous tenderness and

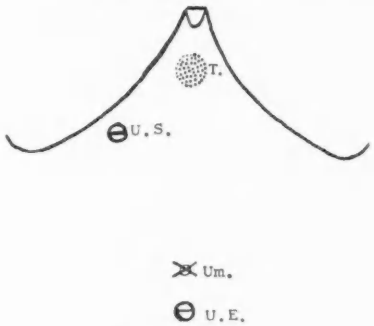

FIG. 7.—Case 24.

hyperæsthesia of the skin also over this area; both in the erect and supine positions the ulcer was situated under this area, its shift upwards being 3 cm. However, its position corresponded neither in the erect nor the supine positions with either of the above maximum points of tenderness, which remained stationary in all positions of the patient.

The other case was decisive, for the tender point on the abdominal wall, which was constant in all positions, was situated in the upper sterno-umbilical line below the ensiform, while in the erect position the ulcer was situated in the mid-line 3 cm. below the umbilicus, and in the supine position it had shifted upwards and outwards for a distance of 9 cm., to a point 5 cm. to the right of the central line (fig. 7).

TABLE II.—POSITIONS OF TWO PYLORIC ULCERS AS DETERMINED BY X-RAYS, AND OF THE TENDER AREAS ON THE SURFACE OF THE ABDOMEN OBTAINED BY LIGHT PALPATION.

No.	Name	Measurements to right of mid-line in cm.		Vertical measurements above umbilicus in cm.		Shift upwards in cm.	Tender areas on the surface of the abdomen, in the erect and supine positions
		Erect	Supine	Erect	Supine		
24	B. W.	0	5	3 below	9	12	Central line—upper
25	J. W. C.	7·5	7·5	9	12	3	Central line—middle; and right costal margin 9 c.c., and diffusely extending to whole of right sterno-umbilicus region

Duodenal Ulcer.

Thirteen Cases (*Table* III).

In all these cases the duodenal cap was reported to be deformed and tender.

Tender areas.—The tender areas were situated in the central sterno-umbilical line in eleven cases, the size of the areas being the same as in the cases of gastric ulcer. In four cases the tenderness was situated in the middle of this line; in four in the upper part below the ensiform; in

Table III.—Positions of Thirteen Duodenal Ulcers as determined by X-rays and of the Tender Areas on the Surface of the Abdomen.

No.	Name	Distance of the base of cap to right of mid-line in cm.		Vertical distance of base of cap above umbilicus in cm.		Shift upwards in cm.	Tender areas on the surface of the abdomen in the erect and supine positions
		Erect	Supine	Erect	Supine		
26	H. B.	4·5	7·2	1·25	3·5	2·5	Central line—whole
27	C. D.	3	4·5	4	8	4	,, upper
28	M. A. W.	2	1	8 (below)	4 (below)	4	,, middle
29	H. C. P.	5	7	4	5	1	,, ,,
30	S. P.	6	6	6	11	5	,, upper and middle
31	A. W.	4	7	4 (below)	0	4	,, middle
32	J. F.	3·5	4·5	4	9	5	,, upper
33	T. H. S.	4·5	5	1	6	5	Central line — upper and middle and right and left costal margin 7 to 9 c.c.
34	H. N.	3·5	4·5	6	11	5	Central line — upper and right costal margin 9 c.c.
35	A. K.	3·75	5	3 (below)	7	10	Central line—middle and right and left costal margins 9 c.c.
36	E. C.	4·5	6	3	9	6	Central line — upper and 4 cm. to left of lower portion of mid-line
37	A. H.	2	3	0	6	6	Right costal margin 9 c.c.
38	H. M.	4	6	0	1	1	,, ,, ,,

two in the upper and middle portions; and in one the whole central line was tender, the maximum point being in the upper part. The area at the 9th right costal cartilage was tender in three (33, 34 and 35) of the eleven cases, and it alone was involved in two cases (37 and 38). The corresponding 9th left costal cartilage area was tender twice in two cases in which the right was also affected. The area to the left of the lower portion of the mid-line was affected once. The tenderness was present in exactly the same positions whether the patient was standing or lying. The areas of tenderness in the duodenal ulcers thus

occupied the same positions as in the gastric ulcers, namely in the middle line, at the costal margins particularly in the region of the 9th costal cartilage, and to the left of the lower portion of the mid-line.

Position of the Ulcer. Patient Standing.

Horizontal position.—The ulcer in every case was situated to the right of the mid-line, the limits being 2 cm. to 6 cm., and the average 3·9 cm.

Vertical position.—The ulcer was level with the umbilicus in two cases; 3, 4, and 8 cm. respectively below the umbilicus in three cases; and in the remaining eight from 1 cm. to 6 cm. above the umbilicus, the average being 3·7 cm.

Patient Supine.

Horizontal position.—In every case the ulcer was situated to the right of the umbilicus, the limits being 1 cm. and 7·2 cm., and the average 5·1 cm.

Vertical position.—In every case when the patient lay down the ulcer occupied a higher position than when he was standing. One was situated level with the umbilicus, one 4 cm. below, and the remaining eleven from 1 cm. to 11 cm. above the umbilicus, with an average of 7 cm. In all the cases, therefore, the ulcer shifted upwards when the patient lay down. The degree of upward shift varied from 1 cm. to 10 cm. with an average of 4·5 cm. In eleven cases the shift was upwards and outwards; in one upwards and inwards; and in one directly upwards.

In these thirteen cases the tender points obtained by light palpation of the abdominal wall were situated at quite different levels from those occupied by the ulcers both in the erect and supine positions. These tender points remained stationary whatever the position of the patient, whereas the ulcer moved upwards in the recumbent position. In those cases in which a tender area at the 9th right costal cartilage is present, the shift of the ulcer upwards and outwards in the supine position carries it in this direction, and so the two kinds of tenderness (clinical and X-ray) may be confused, but careful measurements and the dropping of the ulcer in the erect position, in most cases, are enough to prove that the fixed tender point at the 9th right costal cartilage is in the abdominal wall (figs. 8 and 9).

In view of the statement which has been made [5] that both gastric and duodenal ulcers commonly lie under the mid-line, where the point of maximum tenderness is most often found, R. Trotter has made for

me the following measurements on a separate series of cases, which prove that this statement is incorrect. The exact positions of the ulcer in fifty-two gastric and fifty-one duodenal cases were measured, in relation to the central line of the spine, in radiograms taken in the erect and supine positions at once after a barium meal. The points from which the measurements were taken were the centre of the gastric ulcer, and the centre of the base of the duodenal cap. Only one of the fifty-two gastric ulcers was situated in the mid-line and one within 1 cm. of it in

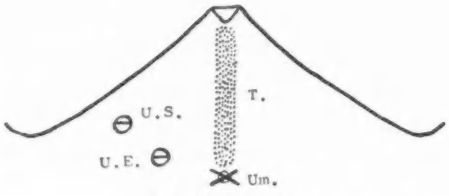

FIG. 8.—Case 26.

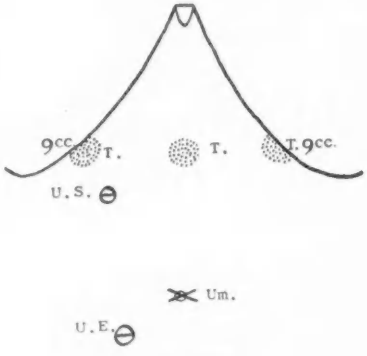

FIG. 9.—Case 35.

the erect position. The remaining fifty were situated to the left of the mid-line, at an average distance of 4·9 cm. In the supine position the ulcers shifted upwards; only one was situated centrally and the remaining fifty-one lay at an average distance of 5 cm. to the left of the mid-line. Of the fifty-one duodenal ulcers six were situated in the mid-line and three within 1 cm. of it in the erect position. The remaining forty-two were situated to the right of the mid-line at an average distance of 2·5 cm. In the supine position the ulcers shifted upwards and usually outwards; one was in the mid-line and four within 1 cm. of it; the remaining forty-six were situated at an average distance of

4·3 cm. to the right of the mid-line. The width of the epigastrium at the level of the transpyloric line varies according to the build of the patient. The average distance from the central line to the costal margin at this point is about 7 cm. Gastric ulcers are, therefore, commonly situated quite as near the costal margin as the central line at this level in both erect and supine positions. The same is true of duodenal ulcers in the supine, but not in the erect position. It may be therefore definitely stated that only a small proportion of either gastric or duodenal ulcers are situated in the mid-line in any position which the patient assumes.

Functional Disturbances of the Stomach.

Thirteen Cases (Table IV).

Certain types of functional disturbance of the stomach give rise to pain indistinguishable in all particulars from that of an ulcer. I have given reasons [6] for assuming that in the absence of complications an ulcer causes pain by acting as a focus of irritation to the neuro-muscular mechanism of the part of the stomach in which it is situated, and its symptoms are due to alterations of muscular tension; these are therefore of precisely the same nature as the symptoms of functional disorder which arise in a similar way. Many cases of functional disorder are operated on in mistake for ulcer; they can be distinguished only by the X-rays, which proves that the stomach is free from organic disease. In this group are thirteen cases and the radiographer reported that there was no ulcer nor tenderness in any part of the stomach or duodenum. All these cases showed tender areas in the anterior abdominal wall in exactly similar positions to, and indistinguishable from, those which I have described in the cases of ulcer.

Table IV.—Tender Areas on the Surface of the Abdomen in Thirteen Cases of Painful Functional Disorder of the Stomach.

No.	Name	The areas occupied the same position in both erect and supine positions.
39	W. S.	Central line—middle
40	E. D.	,, upper
41	L. C.	,, lower
42	A. P.	,, middle
43	B. F.	,, upper
44	S. W. R.	,, upper
45	E. I.	,, upper and right costal margin 7 to 9 c.c.
46	R. S.	,, middle and right costal margin 9 c.c.
47	M. G. H.	,, ,, ,, ,, ,,
48	C. P.	,, upper and 5 cm. to left of lower portion of central line
49	C. M.	Right and left costal margins 9 c.c.
50	M. P.	Right costal margin 9 c.c.
51	D. W.	5 cm. to right and left of lower portion of central line

Discussion.

It is clear from a consideration of these observations that the tender areas present in the abdominal wall in cases of functional disorder of the stomach are of precisely the same nature and origin as those which occur in cases of gastric and duodenal ulcer. They are situated in similar well-defined areas, which are constant in occurrence, are fixed and immobile, and they are associated with the same type of pain although the actual source of the gastric irritation is different. They thus refer to the segment of the stomach affected irrespective of the nature of the irritant upsetting its mechanism. They are independent of any change of position of the patient and thus have no relation whatever to the position of the stomach. They have, therefore, the characters of referred pain and tenderness due to abnormal impulses originating in the viscus, which are conveyed to the spinal cord by its afferent sympathetic nerves, and their positions are determined by the distribution of those muscular and cutaneous nerves in the body wall which enter the same segments of the cord as receive the afferent sympathetic fibres from the stomach.

The following considerations prove that the distribution of the somatic nerves in the wall of the body determine the fixed positions of the pain and tenderness. In the analysis of gastric pain to which I have already referred, I found that a band of pain and tenderness involving the whole of a segmental area of the body wall was uncommon; but that it was usual for the pain to be confined to certain areas, sometimes small in extent, sometimes more diffuse; and it was not uncommon for these areas to be combined, the most frequent combination being an area at the front and another at the back. Although pain is common in the back, tenderness is a great deal commoner in front. The areas of pain are situated in the region of four vertical lines: (1) The mid-line in front; (2) a line through the nipple and costal margin, sometimes in the region of the 9th costal cartilage or sometimes higher up; (3) in the line of the angle and vertebral border of the scapula; (4) the mid-line behind, especially between the scapulæ. In these lines are distributed the terminals of the thoracic nerves, which supply both skin and underlying muscles.

After issuing from the inter-vertebral foramen each thoracic nerve divides into a posterior or an anterior division. The *posterior divisions* divide into internal and external branches which supply the muscles and integument behind the spine. The skin is chiefly supplied by the internal branches above, and by the external branches below the angle of the scapula. The internal branches issue near the spinous processes

and the external branches in the line of the angles of the ribs; the latter also travel downwards for a considerable distance before becoming superficial, and so supply the skin at a lower level than might be expected. The *anterior divisions* of the thoracic nerves pass forwards in the intercostal spaces; the upper ones, from the second to the sixth, become superficial near the sternum, and supply the skin of the mammæ and the front of the thorax; the lower ones pierce the sheath of the rectus, which they supply, and become superficial near the linea alba, but some reach the skin at the outer border of the rectus and supply that on the front of the abdomen. These are known as anterior cutaneous nerves. Each of the intercostal nerves gives off a *lateral*

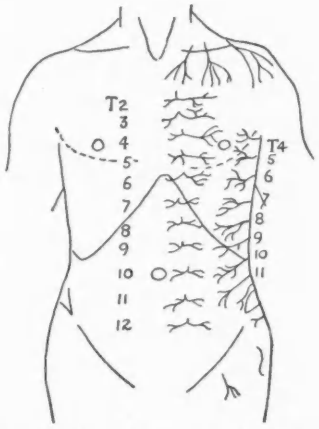

FIG. 10.—To show the terminations of the nerves in the mid-line and nipple line.

cutaneous branch midway between the vertebral column and the sternum, which pierces the muscles in a line a little behind the pectoral border of the axilla: here each divides into an anterior and posterior branch. The *upper anterior branches* pass forwards over the pectoralis major and supply twigs to the skin and the mammæ; the lower anterior branches extend nearly as far forwards as the rectus, and supply the skin in a line with the upper anterior branches. The *posterior branches* pass backwards to the skin over the scapula and latissimus dorsi. A glance at the accompanying diagram (fig. 10) shows that the nerves terminate in the four vertical lines in which pain most commonly occurs.

It is a well-known axiom of medicine that in disease affecting the nerve trunks, at or near their origins, the pain is referred to the

peripheral terminations of the nerves. This distribution of the thoracic nerves is, therefore, quite a satisfactory explanation of the occurrence of the pain in these four lines. But this explanation only holds good if the irritation giving rise to the pain is situated in the spinal cord, or the origin of the nerve trunks at the terminals of which the pain and tenderness are felt. We must certainly assume this to be the case, because the pain and tenderness are segmental in distribution. The fact that pain and tenderness occur in the region of these nerve terminals, therefore, strongly supports the hypothesis that the point of irritation is in the spinal cord. This irritable focus in the spinal cord is clearly due to afferent impulses received through sympathetic nerves from the stomach.

The certainty that in conditions of gastric irritation true visceral referred pain appears does not exclude the probable occurrence of splanchnic pain of a different type as defined by Head [9]. It is not my purpose to say more about this subject, but clearly the tenderness obtained by the radiologist by heavy palpation of the ulcer demands investigation.

Summary.

The observations recorded in this communication strongly support the theory of visceral referred pain as regards the abdominal viscera. The position of referred pain and tenderness due to irritation of the stomach is determined by the distribution of the intercostal nerves; it is the result of disturbance in a certain segment or segments of the stomach; and occurs, therefore, in constant and corresponding positions, whatever is the source of this disturbance.

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TUBEROUS SCLEROSIS WITH EPILEPSY (EPILOIA) IN IDENTICAL TWINS.[1]

BY HOWARD FABING, M.D.

THE similarity of morbid conditions in true twins has always been a source of interest. Neuro-psychiatric disorders hold a peculiar fascination when one of the most crucial of natural experiments is conducted—the making of two persons out of one biological individual. As far back as 1883, Savage [1] reported female twins, aged 28, suffering from similar attacks of melancholia, though they lived apart. Gill [2], writing in the same year, described recurrent maniacal episodes of similar character in 20-year-old female twins.

Epilepsy in twins.—Toledo [3] studied feeble-minded girls, obviously monozygotic twins, who began having seizures at the age of eight years, within a few weeks of each other. He noted further that they had post-epileptic deliria at the same time, even if kept apart. Herrmann [4] reported monozygotic male twins, one of whom began having attacks at 13 years, and the other at 14 years. The pattern of the fits was similar in both. They began with winking, conjugate deviation of the eyes to the left, then upward deviation of the eyes, slow turning of the torso to the left, followed by fall and clonic movement in the major attacks.

Siemens [5] reported dizygotic 8-year-old males. One was very nervous and was described as neurasthenic. The other was quiet. From the age of 5 years onward the former had nervous attacks with tongue-biting. The author regards the case as probable epilepsy. Lange [6] reported five pairs of monozygotic twins, in three of which both had epilepsy, and in two of which one had epilepsy. He added three cases of undetermined zygotism, in two of which both had epilepsy, and in one of which only one had epilepsy.

Whitney [7], in a review of four cases of microcephaly in twins, states that one pair, whose cranial measurements were the same, were idio-imbeciles with epilepsy. One member of another pair in his series also had epilepsy and died in status epilepticus.

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Wilson and Wolfsohn [8] reported homologous female twins. One had "shivering" fits from the age of 3 months to 9 years; after that she had generalized grand mal attacks, and petit mal attacks as well. The other began to have fits at 13½ years, all of which were grand mal in type. They had a similar type of aura: giddiness and queer feelings. Of special interest to our study is the observation that each girl had a pigmented nævus over the right clavicle.

Luxemberger [9] found one case of dizygotic twins in which one had epilepsy. Including Lange's cases, cited above, he collected the following from the literature:—

	Both with seizures	One with seizures
Monozygotic	6	4
Dizygotic	0	7
Undetermined zygotism	3	3

He does not give specific references to his cases.

Olkon [10] observed monozygotic male twins who developed seizures at 20 months, following constipation. A study of their capillary circulation disclosed anomalies which led him to believe that their epilepsy was angiospastic in origin. Under antispasmodic therapy they remained free of seizures for three years.

Legras [11], in a study of psychoses and criminality in twins, reported that he observed two pairs of monozygotic twins, both of whom had seizures; one pair of monozygotic twins in which only one had seizures, and one pair of dizygotic twins in which but one twin was affected with epilepsy. He adds another pair of monozygotic twins, both of whom have epilepsy, seen by H. Lottig, at Nonne's clinic in Hamburg. Talbot [12], in twenty-four observations on the basal metabolic rates of eighteen pairs of twins, mentions one case of epilepsy appearing in ten-and-one-half-year old girls at the same age. Both responded favourably to ketogenic diet.

Sanders [13] reported four pairs of epileptic twins, three of which were monozygotic and one dizygotic. Eighteen-year-old monozygotic females began to have fits within one month when they were 4 years old, followed by a period of remission. One had her first grand mal attack at the age of 14, the other at the age of 15½, after being frightened at a fire. They show no mental deterioration. The father had seizures in his youth, and a maternal aunt has questionable petit mal. Both twins have a large spotted nævus (Unna).

Fourteen-year-old monzygyotic boys began to have seizures at the age of 3, six months apart. The aura in one is the sensation of a globus

followed by a disturbance of consciousness with whistling. In the other, the attacks begin with nausea and he has hallucinations of wheels turning in the right visual field. The attacks which follow are typically grand mal. Both have headache for a long period following the seizure. Both have petit mal attacks in which they talk incoherently. A sibling, as well as the father, have epilepsy.

Twelve-year-old monozygotic females both had their first seizures on the same day when they were $1\frac{1}{2}$ years old. One has had typical attacks since the age of 8 years. She is left-handed and is becoming demented. Her mental age is now 6 years 10 months. The other girl is right-handed and presents no gross mental deterioration. She has had frequent dizzy spells since the age of 4 years. No psychoses nor epilepsy are found in the family. There is twinning in the maternal family. Interscapular telangiectases are present in both.

The fourth pair in Sanders' series were dizygotic and of opposite sex, aged 5. Both began to have fits at the age of nine months, one day apart.

McBroom and Gray [14] reported $8\frac{1}{2}$ year-old monozygotic twin girls who developed seizures at the age of 5 years, one week apart. Originally, the seizure in both girls consisted of only an upward tilt of the eyes and momentary loss of consciousness. One twin has since developed more elaborate seizures, with falling, clonic movements and relaxation of the bladder sphincter. They have no aura, nor any psychic equivalents.

Rosanoff, Handy and Rosanoff [15] surveyed the problem throughout American institutions and found the surprisingly large number of twins with epilepsy as shown in the following table:—

	One with seizures	Both with seizures	Total
Monozygotic males	4	5	9
Monozygotic females	5	9	14
Dizygotic males	12	3	15
Dizygotic females	20	4	24
Dizygotic, opposite sex	32	13	45
	73	34	107

Tuberous Sclerosis.

Tuberose (or tuberous) sclerosis is the name applied by Bourneville [16] in 1880 to a rare form of multiple cerebral sclerosis occurring in young patients who had shown mental deficiency and epilepsy during life. He gave the condition its name from the potato-like appearance

and consistency of the diffusely scattered sclerotic patches. Bourneville also noted the co-existence of primitive tumours of the kidney and of skin lesions described by Balzer and Ménétrier [17] and later by Pringle [18] as adenoma sebaceum, but regarded these as coincidental. In 1895, Cesaris-Demel [19] noted the concurrence of multiple rhabdomyomata of the heart in association with tuberous sclerosis. The condition remained a pathological curiosity, though more detailed histological studies of the brain were made by subsequent workers. Gradually, the clinical syndrome of epilepsy, feeble-mindedness and adenoma sebaceum, associated with tuberous sclerosis, emerged, and in 1911 Sherlock [20] reported nine cases and gave the name "epiloia" to the symptom-complex. His choice in terminology is unusual, and I quote his reasons verbatim :—

> "The term 'epiloia,' coined for the purpose, and having, the writer believes, no existing connotation, is therefore suggested. . . . It has, at any rate, some of the features which, according to Dr. Pye-Smith, characterize a good name : it is short, unmeaning, distinctive, and capable of forming an adjective" (p. 242).

Further studies have been made by Lind [21], Brushfield and Wyatt [22], who reported sixteen cases, Block [23], and others. Recently, Critchley and Earl [24] reported twenty-nine cases, and made a critical review of the literature.

Yakovlev and Guthrie [25], in a paper in 1931, enlarged the concept of this disorder to include congenital ectodermoses other than adenoma sebaceum, viz., Recklinghausen's neuro-fibromatosis and angiomatosis of the brain associated with nævi of the skin in the trigeminal area. They argue that these conditions merge into one another and cannot be sharply demarcated. They found fifty-five of 500 male patients in the Monson State Hospital for Epileptics afflicted with one or more of these three conditions, and state that the condition is probably far commoner than is generally supposed.

Van der Hoeve [26], in 1923, found retinal tumours in both Von Recklinghausen's and Bourneville's disease, and called them phakomata.

Farber [27] has collected forty-two cases of cardiac rhabdomyoma from the literature. Twenty-six showed associated tuberous sclerosis, five did not. In the remaining eleven the brain was not studied. To this total may be added one of Yakovlev and Guthrie's cases of tuberous sclerosis which contained a soft mass in the outer wall of the right ventricle at autopsy. Renal tumours are stated to occur in 80 per cent. of cases of tuberous sclerosis, according to Hyman [28].

This condition, in which we may find sclerotic plaques in the cortex, gliomatous tumours of the choroid plexus and ventricular wall, rhabdomyomata of the heart, primitive tumours of the kidney, tumours of the retina, abnormalities in the skin, its appendages, its blood-vessels and its pigment, associated with epilepsy and feeble-mindedness, has not been reported in twins.

A striking case of epilepsy in twins, studied on the Neurological Service of the Boston City Hospital, appears to fall into this classification.

Case Report.

The patients, Dorothy and Virginia F., have just celebrated their 15th birthday. No cases of twinning are definitely known in the maternal or paternal families, but there is a vague report of twins on the paternal side which cannot be substantiated. The only known epileptic in the family is a maternal aunt, whose seizures began at the age of 30. There are two older sisters, aged 25 and 23. An older brother is aged 18, a younger sister is aged 11. No siblings have died. The girls then are fourth and fifth of six children.

Their period of gestation was normal and they were born easily. Dorothy weighed 5½ lb. and is five minutes older than Virginia, who weighed 5 lb. They sat up, walked and talked at the normal age. When they were 15 months old Virginia had a severe lobar pneumonia, while Dorothy had a mild broncho-pneumonia at the same time. At 4 years they had pertussis, at 5 years they had chicken-pox, and at 6 years they had measles.

Dorothy began to have attacks at the age of 8 years. For a year and a half they were atypical "equivalents"; she would assume a vacant expression, run headlong, grasp something and shake it. On one occasion she shook down a shelf in the bathroom after a running attack and her mother recalls another time when she ran down into the cellar and shook preserves off the shelves in the fruit closet. It was not unusual for her to run to a chair and shake it. The whole episode usually lasted about three minutes. At the age of 9½, these running equivalents were replaced by true convulsive seizures. They now occur about every two to three weeks and are often serial; three seizures in one day is a common occurrence. The aura is a "funny thought." On questioning her closely Dorothy says that her trend of thought suddenly changes and she seems to get a mental glimpse into future events. No hallucinations are associated. She describes this prescience to her mother who chides her for "borrowing trouble." Sometimes she gets the "funny thought" but is able to "fight off" the fit. These are obviously petit mal attacks. The aura is quickly followed by loss of consciousness which lasts five minutes. During the seizure there are typical clonic and tonic movements. She is seldom incontinent of urine and fæces during the attack but often hurts herself in falling. A period of confusion of about three minutes follows the attack.

Virginia's seizures began about a year and a half ago, at the age of 13½ years. They are always nocturnal, occurring usually in the hours after midnight, about once a week. She had an aura of "melancholy," as her mother calls it, for about a half-day before the attack. Her parents, by noticing her glumness and retarded activity, can prognosticate the advent of an attack. Further investigation of the "melancholy" reveals that thoughts of death, God, Christ, and heaven, flit through the girl's mind in a jumbled way, three

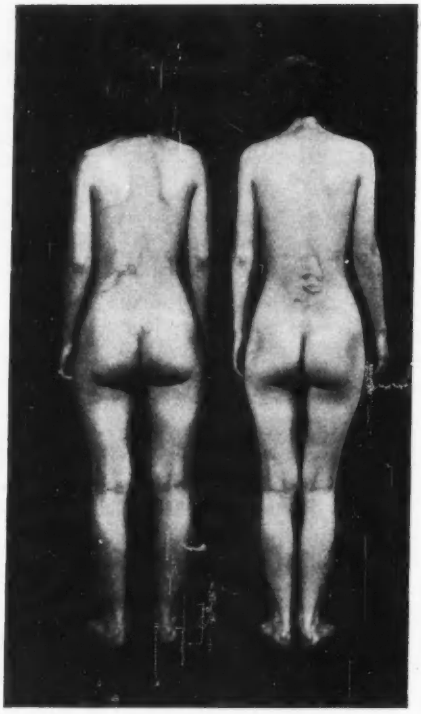

FIG. 1.—Note mirror-image distribution of nævi at the level of L2 spine.

or four times on the afternoon preceding a seizure. Visual, auditory, or gustatory hallucinations are not associated; the episodes are composed solely of abstract thought. They upset her so completely that she often stands with arms outstretched, "like Jesus on the cross," at such times. One afternoon, while they were in the hospital, Dorothy remarked, "Virginia's melancholy to-day. She's thinking about religion again. She's going to have a spell to-night." The seizure occurred.

As Virginia's major attacks occur during sleep, no aura precedes them

immediately. They are evidenced by tonic and clonic convulsions, and she is often incontinent of urine and fæces. Following the seizure, she sleeps until her usual waking time, and has no knowledge that a fit has occurred. She is not drowsy the following day.

The girls are in the first year of high school. They were promoted each year except their first year in grammar school, when illness (measles) kept them from attending school regularly. Virginia does better in school, on the whole, in spite of the fact that Dorothy is much more a "plugger." Virginia's disposition is better; she is less prone to bicker and argue than Dorothy. Virginia is a night prowler; Dorothy sleeps well. Virginia has always been thinner than Dorothy. At the present time their weights are 105 lb. and 115 lb. respectively. Their friends and associates are different, chiefly because the children of the neighbourhood keep away from Dorothy because she has

Dorothy. Virginia.

FIG. 2.—Right facial weakness. Left facial weakness.

fits. Virginia, whose seizures are confined to her bedroom, escapes such social segregation.

The girls are 5 ft 4 in. tall, and are pubescent. Dorothy is the heavier, and is inclined to be somewhat pot-bellied. The integument is of chief interest. They each have a diffuse acneiform eruption on the face which assumes a butterfly distribution. On close inspection, in addition to comedones of acne vulgaris, many small hard red papules are found. These have been present for the past two or three years and defy treatment. Dorothy has a vascular nævus of the capilliary type on the right neck anteriorly. Virginia has two nævi of the same type on her left anterior neck. Dorothy has a series of small pigmented raised nævi on her left back at the level of vertebra L2. Lateral to this is a large nævus anemicus (of Vorner). Virginia has a series of fibromata mollusca at the same level on the right side. Above these is a nævus anemicus of Vorner. In addition, there is a small cluster of nævi of the fibroma molluscum type at the mid-dorsal level on the left.

The only other physical findings of note is a slow irregularity of Virginia's heart. Clinically, this was thought to be auricular fibrillation, but electrocardiogram shows frequent premature auricular beats with aberrant ventricular responses.

The neurological examination discloses facial weakness to emotional stimulation in both girls, Dorothy's on the right, and Virginia's on the left. The remainder of the neurological examination was negative.

LABORATORY DATA.

	Dorothy	*Virginia.*
Urinalysis	Normal	Normal
Blood picture	Normal	Normal
Lumbar puncture—		
Initial pressure	120	165
Colour	Clear, colourless	Clear, colourless
Dynamics	Normal	Normal
Cells	0	1 lymphocyte
Protein	20 mgm. per cent.	20 mgm. per cent.
Gold sol	0000000000	0000110000
Wassermann—		
Spinal fluid	Negative	Negative
Blood	Negative	Negative
Basal metabolism	±0	−10·5 per cent.
Glucose tolerance test	Slight delay in return to normal level	Normal
Intelligence quotient	64	76
X-rays of skull	Negative	Negative
Encephalogram	Within normal limits	The same
Teleoroentgenogram of heart	Normal size and configuration	The same
Fluoroscopic study of heart	No abnormalities	The same
Fluoroscopic study of abdomen	No situs inversus viscerum	The same
Uroselectan study of kidneys	Normal	Bifurcation of right ureter with double pelvis of the right kidney

The immediate family of the twins was inspected for the presence of nævi. The father, the oldest sister (aged 25), the brother (aged 18), the younger sister (aged 11), are all singularly free of any nævi. The mother has a small fibroma molluscum in the left nasolabial fold and two other soft fibromatous tumours in the forehead. The second oldest daughter (aged 23) has a conspicuous melanoma in the intergluteal fold, but is otherwise free of nævi.

COMMENT.

The diagnosis of tuberous sclerosis in these girls is made on the basis of their varied skin lesions, their epileptiform seizures, and their mental

impairment. They have been followed for nine months, and the condition is progressing. They now show more marked facial lesions which look less like acne vulgaris and more like true adenoma sebaceum. That a definite element of deterioration is present in the mental sphere is attested by the fact that Virginia (who was described as the more docile of the two, and whose intelligence quotient was the higher) became such a serious behaviour problem recently that care in an institution became necessary. She split her mother's scalp with a coat-hanger, refused to leave a neighbour's house, threw a stone through a window, and ran away repeatedly. The parents are reconciled to placing the other girl, Dorothy, in an institution also, because she becomes progressively more "bull-headed." Under rather large doses of luminal, seizures have decreased in frequency in both girls.

The cardiac irregularity in Virginia, with the electrocardiographic evidence of frequent extrasystoles arising in the auricles, with aberrant ventricular response, points to a lesion in the conduction mechanism. In the absence of any rheumatic history, and in the presence of tuberous sclerosis, a diagnosis of cardiac rhabdomyoma is not a remote assumption. No cardiac tumour is demonstrable with the aid of the X-ray, however, and the suggestion is advanced modestly, since a study of the literature fails to disclose any previous instance of an ante-mortem diagnosis of cardiac rhabdomyoma. The anomalies discovered in Virginia's right kidney are not inconsistent with a primitive kidney tumour in association with tuberous sclerosis.

The striking mirror-imaging of the skin lesions raises interesting speculations concerning development. The same reasoning may be applied here as in the case of situs inversus viscerum and other mirror-image displacements in identical twins: that the accessory cleavage which divided the zygote into two occurred after polarization of the zygote into right and left halves. If this be granted, the assumption is clear that the lesion which was destined to evidence itself as tuberous sclerosis was present in the very early life of the zygote—shortly after the insemination of the ovum. The temptation arises to assume that the "pre-tuberous sclerosis" lesion was present in the zygote at its beginning, i.e., that the lesion is truly hereditary, or genotypical. However, this is not a necessary deduction, and it may be argued with equal justice that a blastophoric influence—or injury to the zygote—occurred early in its life, and left its mark in the form of tuberous sclerosis.

If a series of dizygotic twins having this symptom-complex could be

studied, the answer to the question of true heredity versus blastophoria could probably be given. If both twins exhibited the disease in nearly equal intensity in all cases, a blastophoric influence, or an intra-uterine environmental influence, would be indicated. If, on the other hand, only one of dizygotic twins exhibited the disease in a series of cases the assumption of genotypical, or truly hereditary, influence would be correct, since dizygotic twins are but siblings, and have differing genoplasm.

In this connection, the only study of nævi in twins is that of Siemens [5] in 1924. He made actual numerical counts of various types of nævi in monozygotic twins, dizygotic twins, and in non-siblings of the same age. He found that the correlation of nævus counts was twice as close in one-egg twins as in two-egg twins, and that the correlation was twice as close in the latter as in non-siblings of the same age. He states, "These findings give us the exact numerical proof that the number of nævi which an individual possesses is definitely dependent on his hereditary anlagen" (p. 24). This, perhaps, is an over-statement.

There is also evidence of mirror-image lesions in the central nervous system in these twins. This is plain when it is recalled that one twin exhibits a right facial weakness while the other shows the same weakness on the left. Furthermore, it is worth noting that the aura of the fit in each girl is a voluminous mental state, indicating that the seizure has its inception in the temporo-sphenoidal lobe in both cases. Whether one girl has a right temporal and the other a left temporal lesion is not demonstrable. To find a parallelism between skin and central nervous system lesions in this condition is to be expected, however, when their common ectodermal origin and common metameric segmentation is remembered. In 1915, Cobb [29] reported a case of hemangioma of the spinal cord at the level of the tenth dorsal segment associated with a series of skin nævi of the same metamere. Other similar instances are quoted by Yakovlev and Guthrie [25].

SUMMARY.

(1) The literature on epilepsy in twins is reviewed.

(2) The syndrome of tuberous sclerosis with epilepsy (epiloia) and allied condition is outlined.

(3) A case of epilepsy in monozygotic twins resulting from tuberous sclerosis is reported.

(4) A diagnosis of probable rhabdomyoma of the heart and primitive kidney tumour in one of the twins is advanced.

(5) The mirror-image position of the skin and central nervous system lesions, similar to situs inversus viscerum and other transpositions frequently found in monozygotic twins, is noted, and from this observation the deduction is made that the anlagen of the lesions of tuberous sclerosis and allied conditions are present in the very early life of the zygote.

(6) The question of genotypical heredity versus blastophoric injury in the production of tuberous sclerosis, as raised by these cases, is discussed.

I wish to thank Dr. William G. Lennox and Dr. Stanley Cobb for the privilege of publishing these observations on their cases, and Dr. P. I. Yakovlev for his interest and assistance.

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A STUDY OF THE MUSCLE CHEMISTRY IN MYASTHENIA GRAVIS, PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY AND MYOTONIA.[1]

By S. NEVIN.

In recent years, the advances which have been made in the study of the chemistry of skeletal muscle have revealed that certain organically bound phosphorus compounds, namely creatine phosphoric acid (phosphagen), adenosine triphosphoric acid (adenyl pyrophosphate), and certain soluble carbohydrate esters, play a very important rôle in the chemical processes subserving muscular contraction. The details of these chemical processes are not yet fully understood; but the changes in the concentration of the phosphorus holding compounds following contraction are well recognized. These changes have been examined in muscle obtained at biopsy from cases of myasthenia gravis, pseudohypertrophic muscular dystrophy and myotonia, with a view to determining the presence or otherwise of any abnormality in the intrinsic chemical mechanism of the muscle in these diseases. Much work of a biochemical nature has been done in the study of these diseases, but this has been confined almost entirely to the examination of substances in the blood and urine related to the metabolism of muscle. The results of these studies have been inconclusive, and they will not be reviewed in detail, but only referred to later in so far as they may be related to the results of the present study.

Basis of the Investigations and Methods of Analysis.

It is essential briefly to outline the chemical changes accompanying muscular contraction, so far as they are at present known, in order that the changes in the phosphorus holding compounds, and their importance, may be better understood.

There are two main chemical processes accompanying muscular contraction, namely, the breakdown of creatine phosphoric acid and the production of lactic acid. In resting muscle creatine phosphoric acid and adenosine triphosphoric acid are present in high concentration, each amounting approximately to 40 per cent. of the total acid-soluble phosphorus. On the other hand, the soluble carbohydrate esters

[1] This work was done during the tenure of a Halley Stewart Research Scholarship at the Neurological Research Unit, National Hospital, Queen Square, London.

(including under this heading glycerophosphoric acid, &c.) are present in small amount. On contraction the earliest chemical change is the anaerobic breakdown of creatine phosphoric acid into its constituents, creatine and phosphoric acid. Adenosine triphosphoric acid also probably breaks down early during contraction into inosinic acid, ammonia and phosphoric acid. Glycogen by enzymic hydrolysis gives rise to hexose. This unites with the phosphoric acid molecules set free in the other reactions to form hexose monophosphate, from which by a series of changes lactic acid is produced. There is thus produced in the contracted muscle a diminution of the creatine phosphoric acid and adenosine triphosphoric acid, with an increase in the soluble carbohydrate esters and in the free orthophosphate. This altered distribution in rabbits' muscle is shown in Table I, from Milroy [1]. These changes

TABLE I.

	Biceps femoris (resting)		Same (after seven minutes' tetanus)	
	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble, P. per g. muscle	1·387	—	1·387	—
Of this:				
As free orthophosphate	0·265	19·1	0·798	57·5
Phosphagen	0·382	27·5	0·057	4·1
Mono-ester	0·198	14·2	0·234	16·8
Adenyl pyrophosphate	0·456	32·8	0·310	22·3
Recovered	1·301	93·6	1·399	100·7

are reversible. Recovery takes place partly anaerobically and is completed aerobically when the creatine phosphoric acid and adenosine triphosphoric acid are resynthesized, while the lactic acid is in part oxidized but largely reconverted into glycogen. The relation of these chemical processes to one another and to the development of tension in the muscle is very obscure and will not be discussed. The importance, however, of the changes in the phosphorus-holding compounds during muscular contraction, especially the breakdown of creatine phosphoric acid, is apparent, and a study of these changes may be presumed to give some definite indication as to the presence or otherwise of any abnormality in the intrinsic chemical mechanism in pathological muscle.

To study pathological muscle the plan of investigation was as follows:—

The affected muscle was exposed at biopsy under local anæsthesia in different cases. A sample of resting muscle weighing approximately 0·5 to 1 g.

was quickly removed and placed in liquid air. The exposed muscle was then thrown into contraction for three to five minutes by faradic stimulation applied locally with silver wire electrodes coated with silver chloride. A portion of this muscle was removed immediately in the contracted state, and another portion after forty-five minutes had elapsed to allow for the recovery changes to take place. These samples were also frozen in liquid air and all three were then analysed for the distribution of the phosphorus-holding compounds. The results were compared with similar experiments carried out in rabbits under amytal and ether anæsthesia, and with the analysis of resting and contracted normal human muscle obtained at operation.

The method employed in the analysis of the muscle was as follows:—

The frozen muscle having been weighed, was extracted with 10 to 15 c.c. of 5 per cent. ice-cold trichloracetic acid after being thoroughly ground with quartz sand in an ice-cold mortar. The extract was filtered by suction into a graduated test tube placed in a freezing mixture, and was immediately rendered faintly alkaline with 40 per cent. NaOH. This extract contained free orthophosphate, creatine phosphoric acid, adenosine triphosphoric acid, and soluble carbohydrate esters. Using Fiske and Subbarow's method of phosphorus estimation, the creatine phosphoric acid and the orthophosphate were determined by precipitation of the latter by 10 per cent. calcium chloride in calcium hydroxide. The adenosine triphosphoric acid was determined by hydrolysis of the original extract for seven minutes in normal HCl at 100° C., the usual calculation then being made, and the soluble carbohydrate esters were calculated by difference from the total phosphorus in the original extract. The calcium precipitate was also examined for insoluble esters other than the readily hydrolysable adenosine triphosphoric acid and when possible the colour development method was also used in the estimation of the creatine phosphoric acid.

Results of Investigation of Normal Muscle.

In the experiments in rabbits the extensor muscles of the leg were used. Contraction was produced for three minutes; forty-five minutes were allowed for recovery. Table II gives an example of the findings

Table II.

	Resting		Contracted		Recovered	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1·766	—	1·659	—	1·641	—
Of this:						
As free orthophosphate ..	0·210	11·9	0·880	53·0	0·202	12·3
Creatine phosphoric acid ..	0·714	40·4	0·108	6·5	0·744	45·3
Adenosine triphosphoric acid	0·763	43·2	0·499	30·1	0·625	38·1
Soluble esters	0·079	4·4	0·172	10·4	0·070	4·3

TABLE III.

	1		2		3		4		5 Resting		5 Contracted		6 Resting		6 Contracted	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid soluble P. per g. muscle	1·245	—	1·261	—	1·212	—	1·328	—	1·159	—	0·905	—	1·170	—	0·960	—
Of this:																
As free orthophosphate	0·191	15·3	0·169	13·4	0·169	13·9	0·148	11·1	0·136	11·7	0·353	39·0	0·131	11·2	0·375	39·1
Creatine phosphoric acid	0·517	41·5	0·515	40·8	0·536	44·2	0·566	42 7	0·502	43·3	0·081	8·9	0·509	43·5	0·135	14·1
Adenosine triphosphoric acid	0·519	41·7	0·564	44·7	0·474	39·1	0·588	44·3	0·514	44·3	0·294	32·5	0·504	43·1	0·253	26·3
Soluble esters	0·018	1·4	0·013	1·0	0·033	2·7	0 026	1·8	0·007	0·6	0·177	19·5	0·026	2·2	0·197	20·5

in several rabbit experiments. The recovery of the adenosine triphosphoric acid and soluble carbohydrate esters was slower than that of the creatine phosphoric acid, and was usually not complete within the time of the experiment.

Through the kindness of Mr. Julian Taylor and Mr. Harvey Jackson, normal human muscle was obtained from the pectoralis major during operations on the breast. Table III gives the results of six analyses. In two cases it was possible to stimulate the muscle for five minutes after removal of the resting sample.

Tables II and III give the normal distribution of the phosphorus-holding compounds in muscle, and the degree of change produced by a given form of stimulation and subsequent to recovery.

Results of Investigation of Pathological Muscle.

A brief clinical summary of the cases investigated is given at the end of the paper.

Myasthenia Gravis.

The biopsy was performed on the right rectus femoris muscle. The muscle was normal in appearance and contracted strongly on direct electrical stimulation. This was continued for five minutes, and forty-five minutes were allowed for recovery. The analyses are given in Table IV.

Table IV.

	Resting		Contracted		Recovered	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of tota
Total acid-soluble P. per g. of muscle	1·395	—	1·218	—	1·090	—
Of this:						
As free orthophosphate ..	0·150	10·7	0·443	36·3	0·135	12·4
Creatine phosphoric acid ..	0·566	40·6	0·163	13·4	0·445	40·8
Adenosine triphosphoric acid	0·538	38·6	0·369	30·3	0·349	32·0
Soluble esters	0.141	10·1	0·243	19·9	0·161	14·8
Insoluble esters	0	—	0	—	0	—

These analyses of the phosphorus holding compounds in this case of myasthenia gravis are of the same order as in normal muscle, and one may therefore conclude that it is improbable that in this disease there is any abnormality in the intrinsic chemical mechanism. If such were present, one would expect some abnormality in the normal phosphorus

distribution in the resting state, and of this there is no evidence, the slight increase in soluble carbohydrate esters being without significance. Further, on contraction by electrical stimulation of the muscle, the changes in the phosphorus distribution occurred to the same extent as in normal muscle and these changes were nearly completely reversed by a period of recovery. It is therefore justifiable to conclude that the chemical processes which accompany activity and recovery in the myasthenic muscle differ in no significant way from those which are characteristic of healthy muscle.

CASE OF MUSCULAR WEAKNESS ASSOCIATED WITH GRAVES' DISEASE.

The biopsy was performed on the right vastus lateralis. The muscle, which was normal in appearance, was stimulated for three minutes, and forty-five minutes were allowed for recovery.

The analyses which are given in Table V show normal chemical changes. The phosphorus distribution in the resting muscle is perfectly normal, and although the changes on contraction are not so great as were found in normal muscle, this is accounted for by the fact that the muscle was stimulated for three minutes only. The high accumulation of soluble esters might be considered abnormal, but their removal during recovery was so complete as to make this improbable.

TABLE V.

	Resting.		Contracted		Recovered	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1·116	—	1·269	—	1·053	—
Of this:						
As free orthophosphate ..	0·104	9·3	0·149	11·7	0·129	12·2
Creatine phosphoric acid ..	0·460	41·2	0·350	27·6	0·430	40·8
Adenosine triphosphoric acid	0·508	45·5	0·465	36·6	0·442	42·0
Soluble esters	0·044	3·9	0·305	24·0	0 052	4·9
Insoluble esters	0	—	0	—	0	—

The relation of this case, on the one hand, to the muscular weakness which is a common symptom in Graves' disease, and, on the other, to the fully developed picture of myasthenia gravis which is occasionally found associated with Graves' disease, is not clear. It is improbable, however, from these biochemical studies, that abnormalities in the

muscle chemistry are the cause of the loss of muscle function in such cases.

Case of Periodic Muscular Weakness.

This case was examined as one of myasthenia, and the chemical findings may suitably be given here, although the histological examination of the muscles makes the true nature of the case uncertain. The outstanding clinical feature of the case was the extreme weakness of the muscles without wasting, especially in the deltoid muscles. The biopsy was performed on the left deltoid, and the plan of the experiment was altered in that after the sample of resting muscle had been removed, the patient was made to contract his muscle as strongly as possible. After a portion of this contracted muscle had been removed, electrical stimulation, which had to be weaker than usual owing to the fact that the main nerve was not blocked, was carried out for eight minutes. This electrically contracted muscle was also examined; the examination of recovered muscle was omitted. The analyses are given in Table VI:—

Table VI.

	Resting		Voluntarily contracted		Electrically contracted	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1·018	—	0·989	—	0·902	—
Of this:						
As free orthophosphate ..	0·118	11·6	0·125	12·6	0·218	24·2
Creatine phosphoric acid ..	0·459	45·1	0·427	43·2	0·238	26·4
Adenosine triphosphoric acid	0·394	38·7	0·406	41·0	0·327	36·2
Soluble esters	0·047	4·6	0·031	3·1	0·119	13·2
Insoluble esters	0	—	0	—	0	—

The resting muscle is seen to be perfectly normal as regards the phosphorus holding compounds, and voluntary contraction has produced only slight chemical changes in these compounds, or such as were reversible during the contraction. On the other hand, weak electrical stimulation has produced considerable chemical change. This shows definitely that in this muscle, which was extremely weak, an abnormal chemistry was not the cause of weakness. The case is of interest as showing the stability of the intrinsic chemical mechanism and how it may be normal in the presence of gross disturbances of muscle function.

Pseudohypertrophic Muscular Dystrophy.

Case 1.—The biopsy was performed on the left soleus muscle. The muscle was paler than normal, and fibrous. Stimulation produced good contraction, and was carried out for eight minutes, when the muscle appeared to be fatiguing. Forty-five minutes were allowed for recovery. The analyses are given in Table VII.

Table VII.

	Resting		Contracted		Recovered	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	0·418	—	0·298	—	0·223	—
Of this:						
As free orthophosphate ..	0·067	16·0	0·059	19·9	0·047	21·1
Creatine phosphoric acid ..	0·137	32·8	0·069	23·3	0·068	30·5
Adenosine triphosphoric acid	0·178	42·6	0·097	32·4	0·085	38·1
Soluble esters	0·036	8·6	0·073	24·4	0·023	10·3
Insoluble esters	—	—	0	—	—	—

Case 2.—The biopsy was performed on the right infraspinatus muscle which clinically showed pronounced pseudohypertrophy. The muscle was extremely degenerated and infiltrated with fat, and only feeble contraction resulted from electrical stimulation. This was carried out for five minutes, and examination of the recovered muscle was omitted. The results are given in Table VIII, and included for comparison is the analysis of resting muscle from a case of muscular atrophy secondary to nerve degeneration. This muscle failed to react to electrical stimulation.

Table VIII.

	Myopathy resting		Myopathy contracted		Secondary atrophy	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	0·079	—	0·089	—	0·359	—
Of this:						
As free orthophosphate ..	0·021	26·6	0·025	28·1	0·102	28·4
Creatine phosphoric acid ..	0·015	19·0	0·012	13·5	0·047	13·1
Adenosine triphosphoric acid	0·028	35·4	0·031	34·8	0·120	33·4
Soluble esters	0·015	19·0	0·021	23·6	0·090	25·1

These analyses of the phosphorus holding compounds in muscular dystrophy show a deviation from the normal in the following respects :— The total acid-soluble phosphorus is extremely low and varies widely throughout the muscle. The creatine phosphoric acid content of the resting muscle is definitely below normal and the breakdown of this substance on stimulation is also less than normal. In the first case the distribution and changes on contraction in the other compounds are not significantly altered, but in the extremely degenerated muscle of the second case, there is a considerable accumulation of soluble esters.

The low total acid-soluble phosphorus is obviously accounted for by the increase of fat and fibrous tissue in the muscle. Regarding the changes from the normal, in the creatine phosphoric acid, it is impossible to make a definite statement. These changes have not been considered indicative of a primary bio-chemical abnormality in the disease but rather secondary to the muscular degeneration for the following reasons :—

(1) If there is in muscular dystrophies a primary failure of the muscle to build up creatine phosphoric acid, it is to be expected that the diminution of this compound in the muscles would be much more considerable than has actually been found. Even in the muscle in the second case, which contains much less than one-tenth of the total acid-soluble phosphorus of normal muscle, there is still 19 per cent. of creatine phosphoric acid.

(2) In atrophied muscle secondary to nerve degeneration, a similar and even greater fall in the creatine phosphoric acid content of the muscle has been found.

(3) Lastly, as shown especially in Case 1, the usual chemical changes in the phosphorus holding compounds take place during contraction, although to a lesser degree, and the creatine phosphoric acid which is broken down is built up again during recovery to nearly its original value ; therefore creatine phosphoric acid can be built up in the muscle ; but why in degenerating muscles it should be much less in amount as compared with the adenosine triphosphoric acid, it is impossible at present to explain.

Case of Dystrophia Myotonica.

The biopsy was performed on the right flexor carpi radialis. The experiment was performed after myographic records had been taken, and it was only possible to examine the resting muscle and contracted muscle after weak stimulation for five minutes. The analyses are given in Table IX.

TABLE IX.

	Resting		Contracted	
	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	0·582	—	0·691	—
Of this:				
As free orthophosphate	0·113	19·4	0·189	27·3
Creatine phosphoric acid ..	0·185	31·8	0·204	29·5
Adenosine triphosphoric acid ..	0·210	36·1	0·192	27·8
Soluble esters	0·074	12·7	0·106	15·3
Insoluble esters	—	—	0	—

These figures for the phosphorus holding compounds of muscle in myotonia also show slight differences from the normal. The total acid soluble phosphorus is below normal, and there is a slight diminution of the creatine phosphoric acid content with less change than normal in this compound on contraction. The other compounds are not significantly altered. Whether these changes from the normal indicate a primary disturbance in the intrinsic chemical mechanism of the muscle or are indicative of some other abnormality of the muscle, excitatory or otherwise, it is impossible to state.

The breakdown of creatine phosphoric acid appears such an important reaction in the chemistry of normal muscular contraction that the change in this reaction found in a disease like myotonia cannot be considered insignificant.

On the other hand the deviation from the normal is not considerable and there is no gross accumulation of one or other compound at any stage of activity. Also, somewhat similar changes have been found in the cases of muscular dystrophy. Therefore it may be that the creatine phosphoric acid mechanism is in some way easily altered by diseased conditions of muscle, although the mechanism itself may not be primarily at fault. This appears the most likely explanation. In any case it seems clear that in the further study of the ætiology of this disease the biochemical investigations must be correlated with electrical studies of the excitation of the muscle.

DISCUSSION.

The results of the above investigations of the phosphorus holding compounds in muscle from cases of muscular dystrophy, myasthenia gravis and myotonia have some relation to the recent work on the metabolism of creatine in these diseases.

In 1929, Brand *et al.* [2] found that the constant creatinuria occurring in cases of muscular dystrophy could be increased 40 per cent. by the administration of glycine and to a less extent by some other amino acids.

Milhorat, Techner and Thomas [3] [4] investigated these changes in more detail, and found that after a period of two to eight weeks the increased creatinuria ceased, and at this stage a considerable clinical improvement took place in the patients. This improvement Milhorat considered might be due to an increased creatine phosphoric acid content of the muscles.

Kostakow and Slauck [5] [6] also suggested from their work on this subject that the underlying disturbance in muscular dystrophy might be the inability to absorb and utilize creatine and that this was restored by glycine, which altered the phosphagen content of the muscles.

Tripoli and Beard [7], discussing the effect of glycine and other amino-acids in muscular dystrophy, state "the creatine retained as phospho-creatine (creatine phosphoric acid) serves over and over again to supply the energy for muscle contraction, and the muscular efficiency of the patient increases at a remarkable rate."

Two questions obviously arise in respect of this work; first, the possible explanation of muscular dystrophy as a disturbance of creatine metabolism and, second, the effect of glycine in the treatment of this disease. With regard to the first question, reasons were given earlier in this paper for regarding the alterations found in the creatine-phosphoric acid in the muscles in this disease as secondary to the muscle degeneration. One ventures to suggest that the alterations in creatine metabolism may be similarly explained. It is probable that creatine is formed in the body at a definite rate, under conditions at present unknown, from specific amino-acids of which glycine is a very important one, and is stored or metabolized almost entirely in the skeletal muscles. In the resting state of the muscle it is mostly found in combination with phosphoric acid, forming creatine phosphoric acid. In adult males all the creatine formed in the tissues is stored or metabolized in the muscle and none appears in the urine. In children some creatine is excreted in the urine and the total creatine co-efficient may be as high as in men. This is due to the production of creatine in excess of the needs of the muscular system at this stage of growth and when the muscular system reaches its average percentage of the total body-weight, the creatinuria ceases. In muscular dystrophy, owing to the excessive degeneration of

the muscle, all the creatine formed in the body cannot be stored or metabolized by the muscles, and some is excreted just as it may be after a recent loss of muscle tissue through the amputation of a limb. Glycine when given in large doses, evidently leads to an increased production of creatine for the time being, and this leads to increased excretion. This effect is not specific for cases of muscular dystrophy and will occur in excessive wasting or disuse of muscles from any cause. It has been found in a case of progressive muscular atrophy (personal examination) to a degree comparable with that which occurs in muscular dystrophy. Further, there is no evidence that in muscular dystrophy there is any such deficiency of creatine for the needs of muscles as would lead to a failure of phosphagen synthesis. In these cases the total creatine co-efficient is generally within the lower limits of normal, indicating rather an excess of creatine which cannot be metabolized by the muscles, and the administration of glycine appears only to add to this excess.

With regard to glycine as a therapeutic agent in muscular dystrophy, some workers have failed to find any improvement (Brand [8]). In those cases in which improvement has been found it is possible that the specific dynamic effects of such large doses of the amino-acid glycine may lead to some stimulation of metabolism in the degenerating muscles, and thereby produce some subjective improvement.

Morgulis and Young [9] deduce, from their study of the creatinuria occurring in a case of myotonia atrophica, that in this disease there is an inability of the muscle to synthesize phosphagen. The explanation given above for the creatinuria occurring in muscular dystrophy also applies here, and the findings given in this paper respecting the creatine phosphoric acid content of the muscles in a case of dystrophia myotonica do not appear to support the view that in this disease there is a failure of the muscle to synthesize phosphagen.

Boothby [10] considered it possible that, as cases of myasthenia gravis excrete small quantities of creatine, the beneficial effects of glycine, presumably from building up the phospho-creatine content of the muscle, would be as likely to occur in this disease as in muscular dystrophy. He has reported considerable success in several cases of myasthenia gravis treated with glycine. In a later paper Boothby [11] reported that there may occur in myasthenia gravis after glycine an increased creatinuria which later falls, and that the clinical improvement may be coincident with this fall.

Remen [12] also found improvement in myasthenia by glycine

therapy, and concluded that in myasthenia gravis there is a disturbance of creatine creatinine metabolism which can be corrected with glycine, and that this disturbance may be a failure of the muscle to build up creatine phosphoric acid. This seems improbable from the results of the investigation of creatine phosphoric acid in myasthenic muscle recorded in this paper. Further, in the case of myasthenia gravis, in which the phosphorus holding compounds were found normal, a considerable increase in creatinuria was produced by glycine; yet apart from the administration of glycine the muscles in this case showed a normal content of creatine phosphoric acid. In this disease, as in muscular dystrophy, these alterations in creatine metabolism appear to be secondary effects of the disease. Also they are less constant in myasthenia gravis; and in a case affected equally to the above-mentioned case as regards the general musculature, no creatinuria was found after glycine. The effect of glycine as a therapeutic agent is another question. If it is beneficial, it is unlikely that it acts through the alteration which it produces in the creatine metabolism.

In myasthenia gravis it would appear therefore that future studies as regards its ætiology should be directed to the investigation of excitatory transmission at the neuro-muscular junction, rather than along metabolic lines. It is at the neuro-muscular junction that ephedrine, the administration of which is commonly followed by some improvement in myasthenia gravis, is most likely to act.

Summary.

(1) The phosphorus holding compounds of muscle have been studied in cases of myasthenia gravis, pseudo hypertrophic muscular dystrophy and myotonia.

(2) In myasthenia gravis they have been found normal, and it has been concluded that this disease is not associated with an abnormality in the intrinsic chemical mechanism of muscular contraction.

(3) In pseudo hypertrophic muscular dystrophy and myotonia some alterations from the normal have been found, the significance of which has been discussed.

(4) The recent work on creatine metabolism in cases of myasthenia gravis, pseudo hypertrophic muscular dystrophy and myotonia has been discussed in relation to the results of the present investigation.

My best thanks are due to Professor T. H. Milroy for his criticism and advice, to the Honorary Physicians at the National Hospital for permission to use their cases, and to Mr. Pennybacker for assistance with the biopsies.

Clinical Summaries of the Cases Investigated.

Case of Myasthenia gravis.

M. O'B., a female, aged 32, was admitted to the National Hospital, under Dr. Carmichael, on February 30, 1932. Three years before admission she began to complain of symptoms of general weakness, which became worse over a period of four weeks, and then persisted with slight variation up to admission. She first noticed difficulty in getting upstairs, then inability to hold objects in her hands, and to raise her arms above her head, then difficulty in sitting up and holding her head erect. Drooping of the eyelids, inability to close the eyes tightly, inability to smile, difficulty in chewing and swallowing, and inability to speak clearly were also complained of. All symptoms were made worse by voluntary action.

On examination, patient showed the typical myasthenic facies, with much facial weakness, extreme weakness of the jaw movements and considerable weakness of all the limb muscles, greater proximally, and also of the neck and trunk muscles. She could not climb stairs, and she had to be helped out of bed.

She was discharged to a convalescent home on October 30, 1932, and remained in the same condition until May 5, 1933, when, following the administration of ephedrine mg. 32 three times daily, she became much better. The improvement was evident on examination, and when the ephedrine was stopped for seven days, at the time of the biopsy on February 24, 1934, there resulted a considerable increase in the weakness of the trunk and limbs.

Case of Muscular Weakness associated with Graves' Disease.

F. P., male, aged 39, was admitted to the National Hospital, under Dr. Carmichael, on May 1, 1934. Three weeks before admission he began to complain of general weakness and exhaustion, and also of occasional nausea and vomiting and loss of weight. His arms felt weak and heavy and he was only able to walk 100 yards. On admission the pulse-rate was 124 per minute, and the blood-pressure 140/60. There was slight fullness of the neck in the thyroid region, fine tremor of outstretched hands and a slight degree of exophthalmos. There was some weakness of opening of the jaw against resistance, some weakness of eye closure and considerable reduction in muscle strength in all movements in the arms and legs.

Case of Periodic Muscular Weakness.

C. H., male, aged 33, has been a patient at the National Hospital, under the care of Dr. Symonds, since February 4, 1927. At the age of 6 years it was noticed that he could not run and play with other boys, and that he stumbled as he walked. From this time he began to complain of periods of general muscular weakness, which would come on suddenly, last for three or four weeks, and then gradually improve. These attacks recurred at intervals of several months, and he is certain that up to the age of 17 he recovered his

strength between the attacks. At this age he commenced heavy work as a butcher, since when he has complained of some general weakness between the attacks, which is always relieved by complete rest from work. During an attack his arms become very weak, and he is not able to carry 6 lb., whereas usually in his work he carries 60 lb. with ease. Also his legs become very weak, and he has great difficulty in getting upstairs.

On examination at a time when the patient felt well there were found slight bilateral ptosis and slight weakness of eye closure. The proximal muscles in the arms and legs were somewhat thinner than the distal muscles, but there was no localized wasting. The strength was generally diminished in the muscles of the arms and legs, more proximally and especially in the deltoid muscles. There was slight hypotonia in the arms and legs. The deep reflexes were all present and equal, but diminished. In the erect posture he stood with considerable lordosis but he rose quickly from the supine position, and had no difficulty in getting upstairs.

A sister of the patient is similarly affected.

The biopsy was performed on March 26, 1934, towards the end of a period of increased weakness.

Pseudohypertrophic Muscular Dystrophy.

Case 1.—P. H., male, aged 14, was admitted to the National Hospital under Dr. Hinds Howell, on November 11, 1933. He was a healthy child until at the age of 6 he began to complain of difficulty in getting upstairs, of rising from the supine position and in running. This weakness gradually progressed in his legs and trunk and affected his arms, so that since the age of 11 he has not been able to stand or walk, but he can still use his arms to feed and wash himself.

On examination there was found extensive wasting of the pectoralis major, the glutei, and the muscles of the arm, back and thigh. Pseudohypertrophy was present in both calves. The strength was extremely weak in all movements.

Case 2.—V. H., male, aged 12, brother of Case 1, was admitted to the National Hospital, under Dr. Hinds Howell, on November 4, 1933.

It is not necessary to describe this case, as the symptoms and progress of the disease and the condition on examination were similar to Case 1.

Case of Muscular Atrophy Secondary to Nerve Degeneration.

J. S., male, aged 69, was admitted to the National Hospital, under Dr. Collier, in January, 1934. Seven years before admission patient began to complain of weakness of his right foot. This slowly progressed and affected the whole leg, and for three years he had had to walk with a stick.

On examination it was found that the right foot was dropped, and that there was considerable wasting of the right anterior tibial muscles, the calf muscles and to a less extent the thigh muscles. All movements at the right

ankle were extremely weak, and those at the right leg and knee noticeably weak. The biceps, knee and ankle jerks were absent in both limbs.

Histological examination of excised muscle showed a condition of simple muscle atrophy of long standing secondary to neural degeneration.

Case of Dystrophia Myotonica.

G. F., male, aged 64, was admitted to the National Hospital, under Dr. Carmichael, on November 2, 1933.

At the age of 27, he began to complain of difficulty in relaxing his grasp in both hands, and at the age of 36, of weakness in his arms and legs, which has gradually progressed. He now has difficulty in walking 100 yards without resting. Weakness of the neck muscles, and slow relaxation of the face muscles after smiling or closing his eyes, have also been complained of.

On examination there was found a myopathic facies, weakness and wasting of the sternomastoids and of the arm and leg muscles generally, with pronounced myotonia in the flexors of the wrist and fingers, and mechanical myotonia in the muscles of the tongue, forearm, thenar eminence, and calf.

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THE VENOUS SYSTEM OF THE VELUM INTERPOSITUM OF THE RHESUS MONKEY AND THE EFFECT OF EXPERIMENTAL OCCLUSION OF THE GREAT VEIN OF GALEN.

BY T. H. B. BEDFORD.

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In an earlier paper [1] an account has been given of a series of experiments on dogs in which the great vein of Galen was occluded at various points on its course to determine if hydrocephalus would develop. Although the animals were allowed to survive for three months none was found at autopsy to have developed this condition. The venous system of the velum interpositum of the dog was also investigated and it was found to differ from that of man. In view of the fact that the effects of experimental occlusion of the great vein of Galen have so far been investigated in no animal other than the dog, it was decided to repeat these experiments using the rhesus monkey. It was hoped to find in the rhesus monkey a Galenic system which resembles more closely that of man. These monkeys are relatively cheap to purchase and they can be kept in good health under laboratory conditions. It is proposed to consider: (1) The anatomy of the Galenic system of the rhesus monkey; (2) the effects which follow experimental occlusion of the great vein of Galen.

(1) The Anatomy of the Galenic System of the Rhesus Monkey.

A careful search through the relevant literature has failed to reveal any account dealing with the anatomy of this venous system. For the purposes of this part of the investigation three rhesus monkeys were used. The findings in these animals were extended and supplemented by observations made on the brains of animals in which the great vein of Galen had been occluded experimentally.

Method.—The animals were anæsthetized and cannulæ were placed in both internal carotid arteries and also in both internal jugular veins. The rhesus monkey, unlike the dog, has large internal jugular veins. The head, with the cannulæ in position, was severed from the body and washed free from blood by injecting warm normal saline solution through

both internal carotid arteries. When the washings were no longer blood-stained, carmine gelatine was injected through both internal jugular veins until the conjunctivæ were found to be coloured. The whole head was then placed in cold running water and allowed to cool as rapidly as possible. When cold, the cranium was opened and the brain fixed in situ in 5 per cent. formol saline solution. If care is taken to discontinue

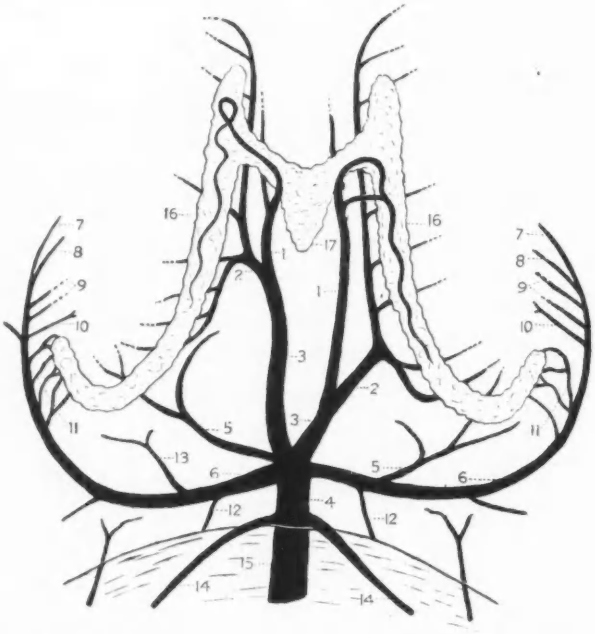

FIG. 1.—Semi-diagrammatic representation of the veins of the velum interpositum and their main communications in the rhesus monkey (control No. 1). In this instance the mode of termination of the basilar veins resembles that found in man. The true relations of the various structures have been distorted and the vessels are depicted as occupying one plane: 1, Vein of choroid plexus; 2, vein of corpus striatum; 3, vein of Galen; 4, great vein of Galen; 5, epithalamic vein; 6, basilar vein; 7, anterior cerebral vein; 8, sylvian vein; 9, striate tributaries of basilar vein; 10, pituitary veins; 11, choroidal tributaries of basilar vein; 12, cerebellar tributary of basilar vein; 13, tributaries from the midbrain to basilar vein; 14, veins from occipital cortex to great vein of Galen; 15, straight sinus; 16, choroid plexus of lateral ventricle; 17, choroid plexus of third ventricle.

the carmine gelatine injection as soon as the conjunctivæ become coloured the mass can frequently be restricted to the venous system. After fixation the brains were dissected in the ordinary way.

One of the most striking features of the Galenic system of the rhesus monkey is its remarkable irregularity. Not only does the arrangement

of the vessels vary from animal to animal but the system is often unbalanced, the one side differing markedly from the other. The Galenic system of the rhesus monkey seems to be even more variable than that of the dog. Fig. 1 is a semi-diagrammatic representation of the Galenic system of the first brain to be examined. The vein of the choroid plexus is a well-defined vessel which receives blood from the choroid plexus of the lateral ventricle and also from that of the third ventricle. Soon after leaving the choroid plexus it is joined by a tributary which receives blood from the anterior part of the corpus striatum. Occasionally this vessel is as large or even larger than the vein of the choroid plexus. After pursuing a course backwards through the velum interpositum for a distance which varies considerably in different brains, the vein of the choroid plexus unites with the vein of the corpus striatum to form the vein of Galen. In one specimen the vein of the choroid plexus failed to join the vein of the corpus striatum and both these vessels terminated separately in the great vein of Galen. The vein of the corpus striatum is a well-defined vessel and is considerably larger than the vein of the choroid plexus. No communications seem to exist between its tributaries and the venous system of the choroid plexus. The veins of Galen run backwards until they reach the region of the splenium of the corpus callosum where, under ordinary circumstances, they unite to form the great vein of Galen. This latter vessel turns upwards round the splenium and ends by becoming the straight sinus at the anterior border of the tentorium cerebelli.

In one instance the veins of Galen did not unite but maintained their individuality until they terminated in the straight sinus. In this animal there was no great vein of Galen. Two pairs of tributaries are usually received by the great vein of Galen near its origin. The first drains blood mainly from the pulvinar but also from the dorsal end of the optic tract, the superior colliculus and the posterior part of the caudate nucleus. A few tributaries may be received from the choroid plexus of the lateral ventricle, but if they exist at all they are very small and of little consequence compared with the vein of the choroid plexus and the choroidal tributaries of the basilar vein. This vessel as already stated usually terminates in the great vein of Galen near its point of origin, but the following variations have been encountered. It has been observed to end in: (1) The vein of Galen; (2) the basilar vein; (3) the under surface of the great vein of Galen close to the point where it becomes the straight sinus. As this vessel appears to drain blood mainly from the surface of the posterior part of the optic thalamus it is proposed to refer to it as the epithalamic vein.

The next pair of vessels to join the great vein of Galen is the basilar veins. From a consideration of fig. 1 it will be observed that in this particular animal the basilar veins resemble very closely those of man. The basilar vein is formed by the union of the anterior cerebral vein and the Sylvian vein. It courses backwards and inwards round the mid-brain, where it is situated below the optic tracts and terminates in

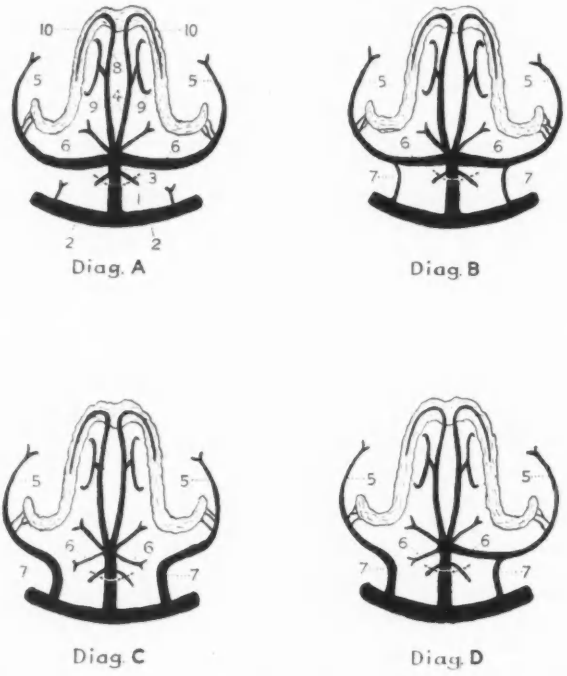

FIG. 2.—Diagrams illustrating variations in the mode of termination of the basilar vein: 1, Straight sinus; 2, lateral sinus; 3, great vein of Galen; 4, vein of Galen; 5, prebasilar vein; 6, superior postbasilar vein; 7, inferior postbasilar vein; 8, vein of choroid plexus; 9, vein of corpus striatum; 10, choroid plexus of lateral ventricle.

the beginning of the great vein of Galen. It receives the following tributaries: (1) A few striate veins near its origin; (2) pituitary veins; (3) inferior choroidal veins from the choroid plexus of the descending horn; (4) numerous vessels from the optic tract and the neighbouring structures; (5) venules from the mid-brain; (6) a few small veins from the superior surface of the cerebellum. A basilar vein of this type was, however, discovered in no other animal. In all the remaining eleven

brains which came to be examined and which included two from control animals and nine from animals in which the great vein of Galen had been occluded experimentally, the basilar vein was found to terminate in a different manner. Some of the various modes of termination of the basilar vein which have been encountered are indicated in fig. 2. Diagram C is a representation of the mode of termination of the basilar vein in the second control animal. It will be observed that here the basilar vein corresponds with that of the first control animal (diagram A) until it reaches the lateral aspect of the mid-brain, when it turns first sharply downwards and then backwards and slightly outwards into the tentorium cerebelli and terminates in the lateral sinus. In this animal the termination of the basilar vein in the great vein of Galen is represented by a small venule which has no direct communication with the more anterior part of the vein. It is probable, however, that communications of a capillary nature are present. The third control animal (diagram B) was found to possess a basilar vein which was not unlike that of the first control in so far as the main flow of blood was into the Galenic system, although a small amount of blood passed directly into the lateral sinus.

For convenience it is proposed to describe by the term "prebasilar vein" that portion of the basilar vein which extends from the point of origin to the lateral aspect of the mid-brain. That portion of the vein which continues from the mid-brain in the tentorium cerebelli to the lateral sinus will be termed the "inferior postbasilar vein," and the vessel which occupies a position which corresponds with the terminal portion of the basilar vein as depicted in diagram A will be described as the "superior postbasilar vein."

The prebasilar vein was constant in all the brains examined, while the superior and the inferior postbasilar veins were variable. It is noteworthy that the inferior postbasilar vein just before entering the tentorium cerebelli receives a number of venules from the anterior aspect of the pons and a well-defined venule from the external geniculate body.

When the brains of the monkeys in which the great vein of Galen had been occluded came to be examined it was discovered that the most frequent arrangement was of the type in which the superior postbasilar vein was very small and had only very feeble or no connections at all with the prebasilar vein, while the inferior postbasilar vein was a large vessel which received the whole of the blood from the prebasilar vein. This was the condition found in the second control animal and is

indicated in diagram C. Occasionally there was a more definite communication between the superior postbasilar vein and the prebasilar vein, but the main flow of blood was almost invariably into the inferior postbasilar vein. In the only exception (diagram D) the superior and the inferior postbasilar veins on the right side received an equal amount of blood from the prebasilar vein, although on the left side the superior postbasilar vein was represented by a minute venule. It was not uncommon to discover a different arrangement on the two sides. It is noteworthy that a main blood flow into the superior postbasilar vein was not found in any of the animals in which the great vein of Galen had been obstructed.

Exception may perhaps be taken to the use, for the purpose of determining normal anatomy, of material derived from animals in which the great vein of Galen had been experimentally occluded, and it may be claimed that the constant presence of a large inferior postbasilar vein in all these animals was due to the post-operative dilatation of small pre-existing communications. It may also be contended that the presence of a small superior postbasilar vein was merely a result of disuse following the occlusion either of the termination of the vessel itself or of the great vein of Galen into which it drains. Although one cannot entirely exclude these possibilities they would appear to be most improbable for the following reasons: (1) As will be pointed out later no evidence could be obtained that the basilar vein takes a special part in the formation of collateral circulation after occlusion of the great vein of Galen in the rhesus monkey; (2) in no instance did any form of spreading thrombosis follow obstruction of the great vein of Galen. In nearly every instance the vessels remained patent almost directly up to the occluding clip. If a large superior postbasilar vein had existed previous to operation it would almost certainly have remained patent and in the brain prepared for dissection it would have been found to contain injection mass; (3) if a small superior postbasilar vein were merely an expression of disuse following obstruction either of the termination of the vein itself or of the great vein of Galen into which it drains, it is difficult to understand why that portion of the vein which joins the great vein of Galen should nearly always have been found to be present, while in many instances it had no obvious connection with the prebasilar vein; (4) two of the brains were obtained from animals in which death had occurred only two days after operation; (5) finally, in one of the three control animals the superior postbasilar vein was represented by a small venule which had no direct communication with

the prebasilar vein, while the inferior postbasilar vein was represented by a large vessel which received the whole of the blood from the prebasilar vein.

The great vein of Galen is joined on its upper surface by one or more venules from the under surface of the corpus callosum, and at the point where it terminates by becoming the straight sinus it is joined by two large veins which drain blood from the under surface of the occipital lobes. In the rhesus monkey the lower border of the falx cerebri contains the inferior longitudinal sinus.

To sum up, it would appear that although the Galenic system of the rhesus monkey may bear at times a fairly close resemblance to that of man, this is not the usual finding. It has been shown that in the specimens examined the basilar vein terminated most frequently in the lateral sinus. In this respect the system resembles that of the dog where this mode of termination of the basilar vein is a constant finding.

The vein of the corpus striatum of the rhesus monkey is characterized by its relatively large size and the extensive area from which it receives blood. Very little blood seems to leave the corpus striatum through the striate tributaries of the prebasilar vein.

With regard to the venous return of the choroid plexus of the lateral ventricle, the bulk of the blood escapes through the vein of the choroid plexus. Some blood also passes from the choroid plexus of the descending horn into the prebasilar vein. It is possible that a few venules connect the choroid plexus with the epithalamic vein. The plexus-like nature of the whole of the venous system of the velum interpositum must however be borne in mind and it is conceivable that communications exist which may escape detection on ordinary examination.

(2) The Effect of Experimental Occlusion of the Great Vein of Galen in the Rhesus Monkey.

The animals varied in age from about two to three years. With one exception they were all males.

Operative procedure.—Anæsthesia was first obtained with ether. Chloralose in a proportion of 0·1 grm. per kilo of body-weight was then injected intravenously and the administration of the ether discontinued. The anæsthesia was maintained by the chloralose. Except for two details the operative procedure was identical with that employed previously for the dog and which has been described in an earlier paper [1]. It was the custom to give the monkeys hypertonic saline solution

intravenously just before opening the cranium so as to obtain a shrinkage of the brain, and after operation a quantity of normal saline solution was injected into the peritoneal cavity. The volume of solution injected into the peritoneal cavity was determined by the amount of blood which had been lost during the operation. By employing this procedure it was found that the convalescent period was considerably shortened. An experiment was deemed successful when after occlusion of the great vein of Galen the animal maintained good health until six weeks later when it was killed.

The venous system of all the brains was injected with carmine gelatine as it was important to determine in each instance the precise anatomy of the Galenic system and if possible the mode of collateral circulation formation. The subsequent treatment of the brains was the same as that which was employed for the dogs' brains in the investigation to which reference has already been made.

Anatomical Changes following Occlusion of the Great Vein of Galen.

The great vein of Galen was occluded in nine monkeys. In two of these death occurred as a direct consequence of operation after two days, and two animals died suddenly in convulsions after a normal survival period of fourteen days. In five instances the monkeys were maintained in good health for six weeks. These were regarded as successful experiments.

None of the animals in which the great vein of Galen had been occluded was found to have developed hydrocephalus, and in most instances the ventricles appeared to be somewhat collapsed. The relatively short course of the great vein of Galen in the rhesus monkey did not permit of much variation in the placing of the occluding clip. In almost every instance the vessels remained patent close up to the fibrous capsule which had formed round the clip. In three of the successful cases the clip had been placed on the termination of the great vein of Galen. In these cases the termination of the superior postbasilar vein in the great vein of Galen remained patent. In one instance the clip was placed on the middle of the trunk and in another on the anterior part of the great vein of Galen. In both these cases the termination of the superior postbasilar vein was occluded.

One of the most striking features of the Galenic system of the rhesus monkey after occlusion of the great vein of Galen was the entire absence of any clear indication of the manner in which collateral circulation had

developed. Except for the presence of the occluding clip, the whole system appeared to be normal. In the three instances in which the termination of the superior postbasilar vein had remained free from obstruction, there was no clear indication that this vessel had taken a special part in the formation of collateral circulation. Similarly the apparently normal appearance of the choroidal tributaries of the prebasilar vein made it seem doubtful if they had served as the route by which the obstructed blood had escaped. The choroid plexuses remained normal to naked-eye inspection. Unfortunately the method employed for preparing the brains prevented rapid fixation of the choroid plexuses, and they were rendered unsuitable for histological examination. The Galenic systems of the four monkeys which failed to survive six weeks also presented nothing of note. No explanation could be found for the onset of fatal convulsions in two of the monkeys.

To recapitulate, it would appear that obstruction of the great vein of Galen in the rhesus monkey, as in the dog, is not followed by hydrocephalus. In the case of the monkey, however, no clear evidence of the formation of collateral circulation could be discovered. The choroid plexuses remained unchanged in their gross appearance.

Discussion.

As a result of the above experiments it may be concluded that under ordinary circumstances a degree of venous obstruction comparable to that which may be expected to follow occlusion of the great vein of Galen in man can only be obtained in the rhesus monkey by the simultaneous occlusion of the great vein of Galen and of the inferior postbasilar vein. Occlusion of the inferior postbasilar vein would present considerable experimental difficulty, for it would be desirable to occlude the vessel without injury to the lateral sinus.

On the other hand it is noteworthy that it was found impossible to discover in what way blood had escaped from the choroid plexuses in the animals in which the great vein of Galen had been occluded. Unlike what obtains in the dog the route through the choroidal tributaries of the prebasilar vein did not appear to have been specially utilized.

It is also important to bear in mind that not only must the route of escape of the blood from the choroid plexuses be considered, but also that of the blood from the greater part of the corpus striatum. It is possible that there is no main channel through which collateral circulation is established, but that the escape of blood is a general process

through the communications of the minute tributaries of the occluded vessels with those of the veins of neighbouring systems. This aspect of the subject requires further investigation.

Since this work was originally undertaken, Dandy [2] has published in book-form an account of his experiences with benign tumours of the third ventricle. This worker obviously regards ligation either of the veins of Galen or of the great vein of Galen as a dangerous procedure and speaking of pineal tumours he says "their operative removal is a far more difficult problem because they are with few exceptions firmly embedded and the veins of Galen both large and small usually pass through the tumour, practically precluding in such instances a successful removal." Unfortunately Dandy does not state whether in any of his cases the tumour interfered with the blood return through these vessels. From a consideration of his description of the findings at operation, it would seem probable that a degree of obstruction to the veins of Galen may have been present in a number of the cases. Dandy's reluctance to divide either the veins of Galen or the great vein of Galen is presumably based on the belief that hydrocephalus or a state of increased intracranial pressure may follow such a procedure. It is noteworthy, however, that in referring to the increased intracranial pressure which is associated with tumours of the third ventricle he states that this condition "was due solely to the obstruction to the pathways through which cerebrospinal fluid finds its exit from the cerebral ventricles." In two cases he was compelled to divide one of the veins of Galen, in another both veins of Galen "had to be doubly clipped and divided." It is significant that no untoward symptoms are reported to have arisen as a result of this procedure in any of these cases.

Summary.

(1) The arrangement and communications of the venous system of the velum interpositum of the rhesus monkey are described. The system is characterized by its extraordinary variability. Although on rare occasions it may bear a fairly close resemblance to that of man this is not the usual finding. The chief difference is in the termination of the basilar vein. This vessel may terminate in the great vein of Galen, but most frequently the greater part of its blood is diverted directly into the lateral sinus.

(2) The great vein of Galen was successfully occluded in five monkeys. None of these animals was found to have developed hydro-

cephalus after a survival period of six weeks. The choroid plexuses appeared normal to naked-eye inspection. A basilar vein of the human type was found in none of the experimental animals. No clear evidence could be obtained of the way in which the collateral circulation had developed. It is suggested that blood may perhaps have escaped through the communications of the minute tributaries of the occluded vessels with those of neighbouring systems.

I am greatly indebted to Dr. Cave, of the Anatomy Department of the Leeds Medical School, for help with the anatomy. I am grateful to Dr. A. D. Macdonald and Mr. S. L. Prescott for help during the operations and to Mr. N. Shtetinin for the drawings.

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AUTONOMIC CONTROL OF THE URINARY BLADDER.

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Introduction.

Before continuing our experiments dealing with the encephalic control of micturition, the first portion of which has already been published (Langworthy and Kolb, 1933), we appreciated the necessity for more exact information concerning the function of the autonomic nerve supply. These observations were to be made upon the same experimental animal, the cat, and were to employ as far as possible the same technical methods. The study of the sympathetic division of the autonomic innervation of the bladder promised to be of particular interest because of Learmonth's suggestion (1931) that a presacral neurectomy might be performed to improve bladder function in case of injury preventing the complete emptying of the viscus.

Animal experimentation offers opportunities for an investigation of the autonomic nervous system not available in clinical work. Denny-Brown and Robertson (1933, B) in their recent study of bladder activity following lesions of the cauda equina and spinal cord were forced from a lack of available material to neglect the function of the intact sympathetic fibres, a function which probably has an important rôle in the explanation of their findings. On the other hand, of course, the experimentalist must base his observations on different objective criteria from those of the clinician. In the animal it is obviously difficult to study the residual urine remaining after micturition; but under anæsthesia it has been shown that the bladder of the individual experimental animal empties on a volume which is remarkably constant. With the preparation under light ether anæsthesia, the present experiments therefore record the volume required for reflex micturition and measure the bladder pressure following the introduction of fluid increments. Moreover, they indicate the amount of fluid held in the bladder under constant pressure.

It may be objected that these mammalian findings are not immediately

applicable to the study of micturition in man. Elliott (1907) indeed states that he could obtain changes in bladder pressure and volume on stimulation of the sympathetics in the cat, but not in certain other mammals even of closely related species. The authors have not extended their studies of bladder inhibition to other forms. From the observations on the bladder of normal human beings, made by Denny-Brown and Robertson (1933 A), it is quite clear that inhibition plays an important rôle. Furthermore, from the standpoint of comparative physiology, one certainly would expect that the same general mechanism of inhibition of bladder activity would be operative in all mammalian forms even though this inhibitory activity was better developed in some animals than in others. While Learmonth's experiments on the sympathetic nerves of the bladder in man and ours upon cats employed such different criteria and technique that they cannot be compared directly, nevertheless they bring out much the same essential facts in reference to the sympathetic innervation.

Methods.

Sixty-one female cats were used as experimental preparations. They were kept under light ether anæsthesia during the operations and subsequent observations of bladder activity.

The apparatus was an amplification of the one employed in previous experiments (Langworthy and Kolb, 1933). A fine glass catheter was inserted into the bladder through the urethra, and the free end attached to the recording apparatus. The catheter was not tied into the bladder, but held in place by the tone of the urethra and sphincters. When reflex micturition began, fluid escaped from the catheter, which became loose in the urethra. The insertion of the catheter without tying prevented the bladder from becoming distended beyond the physiological limits of the experiment.

By means of a three-way tube, the catheter, an open-end manometer of 3 mm. bore, and a burette graduated to $\frac{1}{10}$ c.c. were connected. From the burette water warmed to body temperature could be introduced into the bladder at the rate of about 1 c.c. per minute. Readings were taken after the addition of each 5 c.c. In most of the observations, and especially when the bladder was unusually irritable, the flow was stopped at each 5 c.c. in order that the lowest possible readings could be obtained.

After the introduction of equal increments of fluid, it was possible with such an arrangement of the apparatus to determine not only the

fluid pressure in the bladder during filling and at the time of sphincter relaxation, but also the volume of fluid necessary for the stimulation of micturition. Later, in connection particularly with stimulation of the sympathetic fibres, the importance of determining bladder volume under constant pressure became evident. In order that fluid might enter or leave the bladder freely, an apparatus for such determinations was required to have but little inertia. The simple apparatus that was adopted is shown in the diagram in fig. 1. Removal of the pinch-cock introduced it at once into the fluid circuit previously described.

By means of heavy rubber tubing a large open reservoir was attached to the bottom of one of two 100-c.c. burettes. These were connected across the top by rubber tubing in which was inserted, by means of a

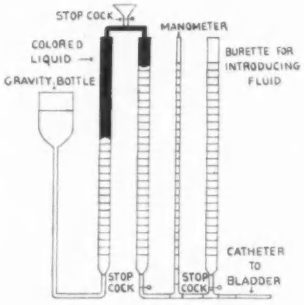

Fig. 1

FIG. 1.—This diagram demonstrates the apparatus used to measure the intravesical pressure after adding equal increments of volume and also to observe the volume of the bladder at constant pressures. A full description is given in the text.

three-way tube, a funnel which could be closed off by a stop-cock. Rubber tubing also served to connect the bottom of the second burette into the system with the manometer and the catheter to the bladder. If constant pressure readings were not desired, this apparatus could be shut off from the remainder of the circuit by means of a pinch-cock on the tubing.

In order to maintain exact pressure readings, a gravity bottle of large diameter and fluid capacity was required. Then by raising or lowering the bottle one could set the bladder pressure at a constant, as indicated by the manometer. Before readings were taken, the constant pressure apparatus was filled carefully with water until no bubbles of air remained. Following this, kerosene stained with Sudan III was introduced at the

top of the burettes from the funnel connecting the tubing until it filled approximately one-half of the burette nearest the gravity bottle and extended to the upper level of the graduations in the second burette. Both tubes were graduated to two-tenths of a cubic centimetre. The coloured fluid acted as an indicator. In later experiments chloroform was added to the kerosene drop by drop until the mixture was almost the same specific gravity as water. With the indicating fluid and the water of similar weights, the constancy of the pressure readings was held more perfectly. Determinations with this apparatus were always begun with the bladder empty. The pressure was then raised and the volume of fluid running in or out of the bladder was subsequently measured on one or the other of the two burettes, depending upon the position of the meniscus, which changed with the direction of the flow of the water. This apparatus, an adaptation of one used by Mortensen and Weed (1934) in their study of the cerebrospinal fluid, was found satisfactory for the present work.

A Comparison of Readings with the Pressure or Volume controlled.

Two graphs in the second figure illustrate the complementary pictures obtained when either the volume or the pressure of the bladder contents are increased in equal increments and the other factor determined. In order to simplify the diagram a sympathectomized preparation with a small bladder and low-pressure readings was used.

Thus in Graph A increments of volume are indicated on the ordinates and the pressures on the abscissæ. The initial pressure with the bladder empty was 0·8 cm. of water. With the addition of fluid the pressure readings remained below 4 cm. until 20 c.c. had entered the bladder. The pressure then rose gradually until the sphincters relaxed reflexly upon 28·5 c.c. of fluid at a pressure of 52 cm. The bladder was then connected with the apparatus for recording bladder volumes at constant pressures.

The results of this second determination are illustrated in Graph B in which the increments of pressure are recorded on the ordinates and the volume of the bladder on the abscissæ. When the pressure was set at zero or one centimetre, no fluid entered the bladder. This was to be expected because in the previous graph the lowest pressure recorded with fluid in the bladder was 1·8 cm. When the pressure was raised to 2 cm. the bladder held 4 c.c., and 14·8 c.c. with the pressure at 3 cm. The bladder contained 20·3 c.c. when the pressure was set at 4 cm.

This gives a very accurate check of the previous pressure readings and illustrates the important fact that the bladder will fill to a great portion of its capacity at a low pressure. With the addition of the next 3 cm. of pressure, there was a small increase in the bladder volume so that at 7 cm. of pressure the bladder held 25·2 c.c., or only 3 c.c. less than the amount required in Graph A to induce reflex micturition. Thereafter the character of the volume increments in the bladder changed markedly. With the addition of further increments of pressure, the volume increase was small and almost a constant factor. In order not

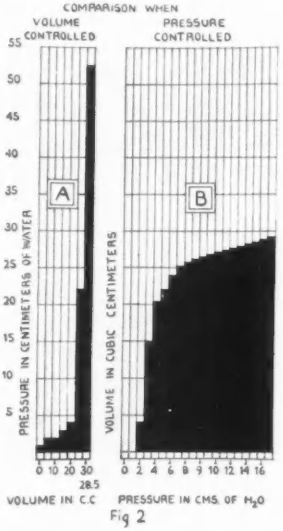

FIG. 2.—Diagram A shows the pressure in a bladder after adding equal increments of fluid, and diagram B the volume of the same bladder when the pressure was increased by equal increments.

to damage the preparation for further study, this experiment was not carried beyond the normal volume required for micturition. At a pressure of 17 cm. the bladder held 28·8 c.c., an amount which had produced reflex micturition in the previous diagram. When the controlled pressure was raised slowly, reflex micturition did not occur at this volume.

Except at the end, when the bladder was filled, the two graphs are complementary. At this time a pressure rise with sphincter relaxation is shown occurring in fig. 2 A, while fig. 2 B shows the volume

increasing by small and fairly equal gradients as the pressure was increased by 1 cm. gradients. The bladder at this stage followed the law of elastic membranes It did not follow this law of elastic membranes, however, until the bladder had been filled with more than 25 c.c. of fluid. Previous to this time its responses were determined by the smooth muscle in the wall of the hollow organ.

Had the pressure been increased by larger gradients, the bladder would have reached its reflex micturition volume and emptied. Indeed when the pressure was set at a high point such as 25 cm. of water, the bladder would alternately fill and empty an indefinite number of times.

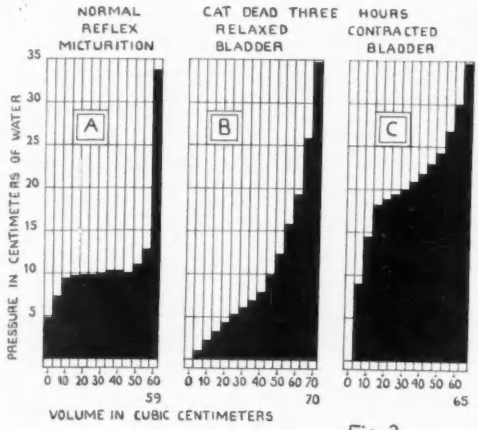

Fig. 3

FIG. 3.—Diagram A gives the intravesical pressure of a normal bladder after the addition of increments of volume, and diagram B the pressure in the same bladder with the muscle relaxed three hours after removal of the bladder from the body. The reading in diagram C was made when the muscle of the incised bladder was tightly contracted.

In the present case the very slow raising of the pressure defeats the normal reflex of micturition. Micturition is initiated by waves of bladder contraction which finally become fused in a constant tonic contraction. When the pressure is held constant at a low level these waves are suppressed and are unable to break through to initiate the emptying reflex.

Figure 3 shows the pressures after the addition of equal fluid increments to the normal cat's bladder under dial anæsthesia (Graph A). The pressure readings were extremely constant, as they are with this type of anæsthetic, and until the bladder was nearly filled remained

around 10 cm. of water. Thereafter the pressure rose and the bladder emptied reflexly at a pressure of 33·7 cm. and a volume capacity of 59 c.c. The cat was killed, the bladder removed from the body, a catheter tied in the urethra and the organ placed in warm saline solution. Three hours after the removal of the bladder, another reading was made; the muscle at that time was relaxed and the pressure readings after the addition of fluid are recorded in Graph B. With the addition of the fluid increments, the bladder pressure rose by fairly equal increments until the bladder was almost completely filled. After reaching the reflex emptying point of the normal animal, the pressure rises became progressively greater. The bladder was obviously near the limits of capacity at 55 c.c.

The smooth muscle of the bladder wall was still responsive, a strong contraction occurring when the fluid was expressed through the catheter. The viscus then was tightly contracted; a reading was made which is recorded in Graph C. When the first increments of water were introduced, the pressure rose steeply, but as the bladder became distended with fluid these rises became smaller, so that they resembled the rises recorded for the relaxed bladder in Graph B. After the bladder became distended to that volume effecting micturition reflexly, the increments of pressure-rise again increased in size.

These charts show that pressure in the dying bladder increases by graded increments, and there is, moreover, a loss of that adaptation by which increasing amounts of fluid are held at approximately the same pressure. The suggestion will be made later in this paper that Graph B of the relaxed bladder resembles the bladder musculature behaviour following sympathectomy, and Graph C of the contracted bladder has some resemblances to the condition observed after parasympathectomy.

These graphs also indicate that the bladder has a size which is relatively constant for the individual, and that reflex micturition under anæsthesia occurs when this volume is reached. The bladder volume is not at once diminished by section of the sympathetic nerves, but on the contrary the reduction is gradual. Similarly the bladder does not immediately expand because of the loss of tone resulting from section of the parasympathetic innervation. In this case the wall is probably stretched passively by the accumulation of fluid which it cannot expel. Similarly, the dead bladder shows approximately the same volume as does the live, and when this volume is reached or exceeded the pressure rises markedly with further addition of fluid.

Stimulation of the Sympathetics.

Following sympathetic stimulation in the cat, Elliott (1907) reported inhibition expressed as either a decreased bladder pressure or an increased bladder volume. This was one of the few convincing reports in the literature. Inasmuch as his findings were not expressed in terms of the technique of the present work, the stimulation was repeated in many of our experiments. This supplied new information concerning the changes in bladder pressure or volume which could be obtained at

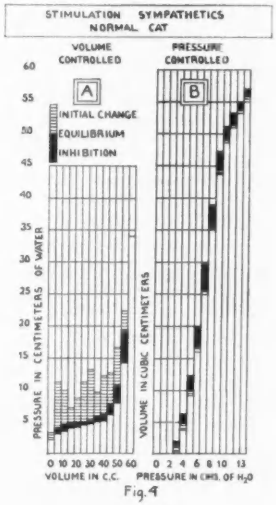

Fig. 4.—Graph A shows the effect of stimulation of the sympathetics upon the pressure of fluid in the bladder of the normal cat at different stages of filling: Graph B demonstrates the change in volume of the vesical contents on sympathetic stimulation. The initial effect of stimulation is indicated by the cross-hatched area and the relaxation by the black rectangle. The line between indicates the reading before stimulation.

different stages in the filling of the viscus. The current was supplied by means of a simple Harvard inductorium connected to a shield electrode which caught together the sympathetic fibres of the two sides. The construction of the electrode prevented the escape of current to adjacent structures. At first the hypogastric nerves were freed and caught in the electrode, but later on it was found more satisfactory to include both sympathetic trunks just above the emergence of the hypogastric nerves. The pressure changes were recorded after the addition of 5 c.c. fluid increments, and again after increasing increments of

pressure were applied to the bladder contents. The two types of results are shown in Graphs A and B in fig. 4.

After the fluid increments had been added to the bladder, the pressure was allowed to fall to the lowest level possible, and then this pressure was recorded. In every case stimulation of the sympathetics at this time caused a quick and non-sustained rise of bladder pressure followed by a fall below the lowest reading obtained before stimulation. This fall was slow and the relaxation occurred after a definite latent period which was occupied partially by the initial contraction. When the stimulus was removed, the pressure rose slowly, and after fifty seconds reached the point recorded before stimulation. In Graph A the middle line or the upper level of the black rectangle represents the lowest pressure recorded before stimulation, the cross-hatched area above shows the height of the initial rise and the black rectangle the fall of bladder-pressure which followed the stimulation.

The intravesical pressure of the empty bladder was recorded at 2·2 cm. (fig. 4, Graph A). Stimulation of the sympathetics elevated the pressure to 3·1 cm.; no relaxation could ever be demonstrated with the bladder empty. The addition of 5 c.c. of fluid raised the bladder pressure to 4 cm. of water. Sympathetic stimulation at this time elevated the pressure to 11·2 cm., and then lowered it to 3·3 cm. Until more than 30 c.c. of fluid had been introduced, the pressure of water in the bladder remained between 4 and 5·1 cm. Throughout this phase of the experiment the rises following sympathetic stimulation showed variations of no particular significance. As the fluid volume was increased, the relaxation, on the other hand, tended to become less marked. When, however, it is realized that the bladder before stimulation is holding an increasing quantity of fluid at approximately the same pressure, then the occurrence of such a tendency might well be expected.

Elevation of the bladder volume to 40 c.c. effected a rise in pressure to 6·2 cm., and stimulation increased the amplitude of relaxation to 0·8 cm. Then, with the increasing fluid volume in the bladder and the higher manometer readings, the amount of pressure fall obtained increased markedly, so that it was not a fraction of a centimetre, but instead several centimetres. Indeed, with 50 c.c. of fluid in the bladder, the relaxation amounted to 5 cm. The bladder emptied reflexly on 60 c.c. at a pressure of 34 cm. As far as the pressure readings are concerned, the inhibitory effect of sympathetic stimulation becomes vastly greater as the bladder is approaching the limits of its capacity. As the bladder

becomes distended, the initial rises become somewhat smaller; these rises on sympathetic stimulation never caused fluid to escape from the urethra.

We turn now to the complementary picture showing the volume changes on sympathetic stimulation with the pressure increased by one centimetre increments. These readings were made on the same preparation as those charted in Graph A (fig. 4). In Graph B the middle line at the lower edge of the black rectangle represents the normal reading, the bladder volume before stimulation occurred. The cross-hatched block indicates the fluid which ran out of the bladder at the beginning of stimulation, while the solid black area signifies that volume of fluid entering when relaxation occurred. As would be expected, fluid failed to enter the bladder at 1 or 2 cm. of pressure, because the pressure in the empty bladder measured 2·2 cm. At a pressure of 3 cm. the bladder held 2·2 c.c. of water. Stimulation caused 0·7 c.c. of fluid to leave the bladder, and then effected a 0·7 c.c. increase above the original volume. After relaxation became effective, fluid entered the bladder slowly, and about a minute after stimulation ceased the bladder regained its original volume. The amount of water leaving the bladder on initial stimulation remained less than 1 c.c. and decreased in amount as the viscus reached its capacity. The volume of fluid entering the bladder with relaxation increased, became maximal when the organ was half full and then, as it reached the limit of its capacity, decreased in amount. At a 7 cm. pressure and a 21·6 c.c. volume, the amount of fluid added to the volume by stimulation of the sympathetics was 4 c.c.

The greater relaxation of pressure in Graph A was obtained when the bladder was approximating the limits of its capacity. The second chart, B, makes it clear on the other hand that this marked change in pressure does not mean that the greatest increase in volume can be induced on sympathetic stimulation at this time. The increase in volume is greatest when the bladder is moderately filled. Then a slight decrease in pressure allows a large quantity of fluid to enter the bladder. When the bladder is full a marked change in pressure is related to only a small change in volume. Evidence that sympathetic stimulation effects a more marked relaxation when the parasympathetic fibres have been thrown out of function will be forthcoming later on in this paper.

The Effect of Removal of the Sympathetic Innervation of the Bladder.

No one, as far as the authors are aware, has studied experimentally the effects upon bladder pressure and volume resulting from section of

the sympathetic nerve supply. It is true that Learmonth states that a transient frequency follows the operation in man, but in his clinical cases he gives no clear explanation of the functional improvement following section of the sympathetics. The present experiments show that it would not be possible to evaluate and analyse accurately the results of sympathectomy unless pre-operative studies of normal bladder function are made.

In the present experiments the sympathetics were approached retroperitoneally through a left lateral incision. In the earlier studies,

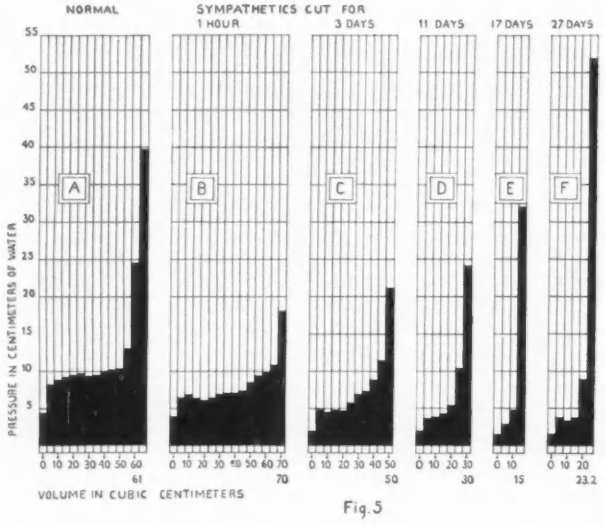

FIG. 5.—This diagram shows the pressure and reflex volume in the bladder just before and after section of the hypogastric nerves and the decrease in volume following the operation. Note the effect of the section upon the pressure at which the sphincter relaxed.

the hypogastric nerves were isolated and removed, but later on, to avoid the possible regeneration of these fibres, both lumbar sympathetic chains were exposed and taken out along with the ganglia.

The striking results of these experiments are perhaps best presented by discussion of the graphs. The effect of section of the sympathetics upon the pressure at which the sphincters relaxed was not observed in all of the cases; an example in which the sphincter changes are apparent was chosen for the first demonstration. Graph A in fig. 5 shows the pressures in the normal bladder after the addition of fluid increments.

This bladder emptied reflexly at a fluid pressure of 39·8 cm. and a fluid volume of 61 c.c. The bladder pressure remained below 10 cm. of water until the viscus was almost completely filled. After the sympathetics had been removed and the wound closed, a second determination showed the bladder to have a capacity of 70 c.c. instead of the former 61 c.c. This slight increase in bladder capacity, which is seen immediately after section of the sympathetics, is probably dependent on the long period of the anæsthesia and the shock of the operation. The sphincters which relaxed in the normal cat at a pressure of 39·8 cm. now relaxed at 18 cm.

The next three graphs (C, D and E of fig. 5) show, during the first three weeks after the operation, a progressive decrease in the volume required for reflex micturition and a progressive increase in the pressure at which the sphincter relaxed. Thus, the reflex capacity was 50 c.c. on the third day, 30 c.c. on the eleventh day, and only 15 c.c. on the seventeenth day. The pressure at which the sphincter relaxed rose to 21 cm. on the third day, 24 cm. on the eleventh day, and 32 cm. on the seventeenth day. The effect upon the pressure at which the sphincter relaxed was observed immediately after the operation, if at all, and was only transient. The change in reflex capacity of the bladder was constant and developed slowly over a period of days or weeks. When the sympathetics had been removed, the bladder held increments of fluid at lower pressures than it did in the intact preparation. The initial reading with the bladder empty was lower, 2 cm. rather than 4·3 cm. in the normal cat. Moreover, the bladder was less irritable to stretch stimuli and less spontaneous waves were seen. As the bladder was distended with increments of volume, the pressure rises increased by a series of steps, and there was less tendency for an accommodation of varying volumes at the same pressure than was found in the normal bladder. With increased volume the successive increases in pressure are of course accentuated by the fact that the bladder has become smaller in size. The pressure rises resemble those seen in the dead relaxed bladder shown in Graph B of fig. 3.

At the end of twenty-seven days, the bladder pressure at the time of sphincter relaxation was greater than in the normal preparation, 52 cm. as opposed to 39·8 cm. The reflex capacity was greater than ten days before, 23·2 c.c. instead of 15 c.c. Further studies, not shown in the figure, demonstrated a further progressive increase in the volume required for reflex micturition, so that on the forty-eighth day post-operatively the bladder held 45 c.c. at a pressure of 48 cm. of water.

It held approximately two-thirds of the volume of the normal viscus. In this animal the hypogastrics had been cut, and it seemed not unlikely that the sympathetic fibres had regenerated. Therefore on the forty-eighth day after the first operation the abdominal sympathetic trunks were exposed and removed bilaterally. Again the pressure at which the sphincter relaxed decreased at once and the bladder became progressively smaller. On the tenth day after the second operation the bladder emptied at 22·5 c.c. with a water pressure of 30 cm. Soon afterward the cat died of a respiratory infection, ending the experiment prematurely.

The other studies which will be reported now avoided this possibility of sympathetic regeneration, at least to a much greater degree, because the sympathetic chains were removed either unilaterally or bilaterally in one piece from the lower surface of the diaphragm to the sacrum.

The bladder capacity required for reflex micturition under anæsthesia varied enormously from one animal to another, although remarkably constant for a single normal animal. The values range from 12 to 260 c.c., and although this variation depended to some extent upon the age and size of the cat, by no means were these the most important factors. It had also a relationship to animal behaviour and activity; very irritable and excitable animals in general had small bladders. It perhaps also had to do with previous habit training. Subsequently it will be shown that large bladders are more markedly influenced by section of the sympathetic nerve supply than are medium-sized or small bladders.

In certain of the experiments, the abdominal sympathetic chain was removed unilaterally and the resulting bladder capacity determined; later, when the capacity had remained relatively constant for weeks, the second sympathetic chain was cut. A description of typical experiments will indicate the results obtained.

Two of the preparations had bladders of unusual capacity, 235 c.c. and 230 c.c. In both cases the volume dropped to less than half the original amount five days after the operation, and in fifteen days to less than one-fourth of the original amount. In one the reflex volume continued to decrease in size to 26 c.c. on the thirtieth day post-operatively. During the fourth week the capacity of one of the bladders took an upward swing and remained about 80 c.c. On the thirtieth day following the first operation in one case and on the thirty-fifth day in the other, the second sympathetic chain was removed. The smaller bladder then maintained the reflex capacity of 30 c.c., while the reflex volume of the

other decreased to 47 c.c., its smallest volume after the first operation. These animals were followed for seventy days after the first operation. At the end of this time one bladder had a reflex volume of 28 c.c., the other of 46 c.c.

Another experiment tested bladder capacity after unilateral and then bilateral sympathectomy in a cat which originally had a bladder of medium reflex volume, 89·5 c.c. At the end of the third week after operation, the bladder reached its smallest reflex size of 20 c.c. Then there occurred a slow increase in volume which led to a bladder capacity of 48 c.c. during the sixth week. With the bladder capacity fairly constant, the second abdominal sympathetic chain was removed. The capacity fell again to 20 c.c., the lowest reading previously recorded, but thereafter became elevated and remained constant at the same level at which it became stable following the first operation.

It is clear that the decrease in bladder capacity is as great after unilateral sympathectomy as it is when both sympathetic chains are removed. For normal sympathetic inhibition then, it is essential that the bilateral innervation be intact.

It is interesting to compare the effect of bilateral sympathectomy upon the bladder capacity of two animals possessing a marked difference in normal reflex volume. The bladder of one had an initial capacity of 120 c.c.; of the other 30 c.c. On the fourth day after the operation, the reflex capacity of the large bladder decreased to 30 c.c., and then following a fluctuation of increased volume reached a 21-c.c. capacity on the forty-sixth day post-operatively. The bladder with the original 30 c.c. capacity was reduced to 5 c.c. on the seventeenth day, but increased in size slowly to a peak of 23 c.c. on the thirty-fifth day. The volume then slowly decreased again. The final readings were made on the seventieth day after the operation. At that time the capacities of the two bladders were practically equal, 16 and 22 c.c.

After removal of the sympathetic innervation, the greatest diminution in volume is obtained in the bladder, which requires the largest normal volume for reflex micturition. A small bladder may show a considerable decrease in size after sympathectomy, but later its volume tends to approach although not to reach the normal. After sympathectomy, the bladders of the experimental preparations tend to approximate a mean capacity of from 20 to 50 c.c.

In two animals of our series the results deviated from those previously described. After unilateral sympathectomy, the reflex capacity in one of the cats became greater than normal, but after the removal of

the second sympathetic chain the volume of this bladder was reduced to less than the normal reflex capacity. The second cat showed a decrease in reflex capacity after unilateral sympathectomy, a decrease, however, that was not maintained, the volume increasing eventually to normal. Although the decrease was not striking, removal of the second sympathetic chain lowered the volume below the normal amount. These results indicate the variations in sympathetic control of the bladder in different preparations.

The decrease in size of the bladder after sympathectomy could be demonstrated by abdominal palpation. The cat has a very long urethra and the bladder normally lies high in the abdomen. After sympathectomy the bladder is pulled down into the pelvis and remains in this position almost constantly.

The Effect of Section of the Parasympathetic Nerves to the Bladder.

Two types of operations were used to cut the parasympathetic fibres. The spinal canal was opened and the sacral roots cut near their origin from the cord or the sacral cord was removed if a bilateral effect was desired. In the other method, the second, third and fourth sacral roots were isolated in the pelvis. A bilateral operation of the second type required two incisions; the sciatic nerve was followed into the pelvis, the roots isolated by careful dissection and cut. The results of these two procedures were similar and no further distinction will be made. The approach into the spinal canal is undoubtedly the easier. Both of these sections paralyse the internal pudendal nerve.

The results of unilateral section are recorded in fig. 6; reflex micturition in the normal preparation under ether is demonstrated in Graph A. The cat's bladder emptied reflexly on a volume of 48 c.c. at a pressure of 44 cm. The sacral nerves were then cut upon one side. In three days a second determination was made and the bladder was found to be larger than formerly, for it held 70 c.c. and relaxed at 38·2 cm. A period of twenty-one days from the time of operation was then allowed to elapse before a second reading was made. At that time the reflex capacity had decreased to less than its original size, so the bladder emptied on a volume of 33 c.c., and at a pressure of 42 cm. These changes in bladder capacity are characteristic of parasympathetic lesions whether the injury is unilateral or bilateral. For a few days after the operation the bladder volume is increased, but later it shrinks to something less than its original size.

After unilateral injury of the parasympathetic fibres, the cats failed to show any evidence of incontinence and apparently emptied the bladder quite normally. On the other hand the bladder wall became thickened as evidenced by palpation and by post-mortem examination. Although this change involved both sides of the bladder there was an evident difference on the two sides, the thickening being definitely greater on the paralysed side.

For a comparison of the effect of unilateral and bilateral parasympathetic lesions, the sacral cord was then removed in the same preparation: the results are shown in fig. 6 (Graphs D and E). When

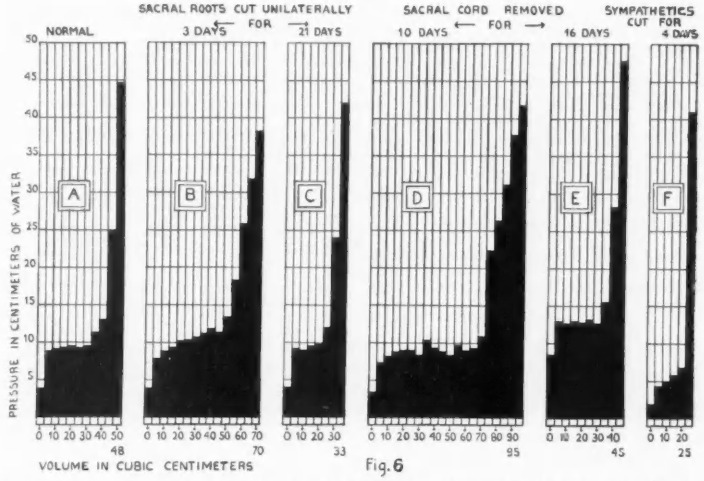

FIG. 6.—This figure shows the effect upon bladder volume and pressure of unilateral and then bilateral section of the parasympathetic fibres. Afterwards the abdominal sympathetic chains were removed and the result is shown in diagram F.

the first reading was made, ten days after removal of the sacral cord, the bladder held a large quantity of fluid, 95 c.c. as compared with 48 c.c. in the intact cat (Graphs A and D). The type of diagram used here affords an inadequate picture of the bladder behaviour at this time. The muscle was irritable and responded with very marked contractions to the stretch caused by the addition of fluid. These contractions were largest early in the filling of the viscus and decreased in size as the bladder neared the limits of its capacity. The waves of contraction increased the pressure in the bladder as much as 14 cm. The intravesical pressure remained high after the introduction of fluid, and it was

necessary to wait some time to obtain the lowest possible readings. Moreover, the muscle was sensitive to ether and an increase in the depth of the anæsthesia caused a pressure rise. When the bladder was filled it did not empty, instead only a few drops of fluid escaped from the urethra. The viscus at this time showed the late stages of paralysis following bilateral lesion of the parasympathetics. Although small quantities of fluid escaped from time to time when the bladder was full, the contraction of the wall was not sufficient to expel the fluid. At frequent intervals the bladder had to be emptied manually.

After the operation, the function of the lower bowel was abnormal; the rectal sphincter was widely dilated and the mucosa everted. Marked constipation persisted and presented one of the greatest obstacles in caring for and preserving the animals.

A second determination of bladder capacity was made sixteen days after removal of the sacral cord when automatic micturition had become established (Graph E, fig. 6). During the six days following the last reading, a great decrease in bladder volume had occurred. After the development of automatic micturition, the bladder capacity usually becomes slightly less than that of the normal cat; the bladder now emptied on 47·5 c.c. at a pressure of 48 cm. The bladder muscle was now even more irritable than at the time of the previous reading. Increase in the depth of the anæsthesia caused contractions of the muscle, and the introduction of fluid increments elicited waves of contraction in response to the stretch of the muscle. After the introduction of fluid the intravesical pressure was always high and the lowest obtainable readings exceeded those recorded at previous times upon the same bladder. The initial pressure with the bladder empty was 8·5 cm. of water.

The cats with the sacral parasympathetics removed were a great nursing care. After automatic micturition was developed they were always wet and the perineum was œdematous. Usually the bladder became infected shortly after catheterization was started, and this infection was difficult to control. In our experiments bladder infection was almost pathognomonic of parasympathetic injury, for it seldom occurred in the other animals. One of the principal technical difficulties arose from the stasis of the gastro-intestinal tract and the resulting anorexia.

Palpation of the bladder through the abdomen revealed a thickening of the wall. This change in the bladder musculature was marked, when the organ was examined post-mortem.

Stimulation of Sympathetics of a Cat with Automatic Bladder after Parasympathectomy.

Stimulation of the abdominal sympathetic chains in a cat with an automatic bladder following parasympathectomy gave more striking results than stimulation in the intact animal. Inasmuch as any increase in the intake of ether caused a contraction of the detrusor muscle, the anæsthetic was administered through a tracheal tube by means of an artificial respiration apparatus, and every effort was made to keep the anæsthetic constant. In Graph A of fig. 7 the equal increments of

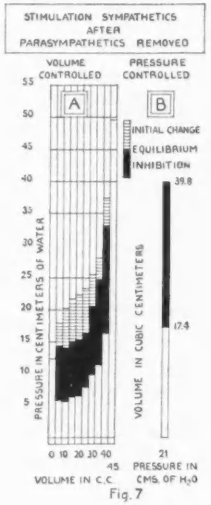

Fig. 7

Fig. 7.—The effect of stimulation of the sympathetic chains upon pressure or volume in the bladder which is automatic after section of the parasympathetics is shown in this diagram. The black rectangles indicate the extent of the relaxation and the cross-hatched areas the initial rises in pressure.

volume are recorded on the ordinates and the pressure readings on the abscissæ. The upper edge of the black rectangle records the lowest pressure readings obtainable at a given volume before stimulation. The cross-hatched areas indicate the initial rise in pressure following stimulation and the black cylinders show the diminution of pressure which ensued. The pressure readings before stimulation are, of course, abnormally high; this is characteristic of the automatic bladder. Stimulation induced a quick rise of pressure which was followed by a slow fall to a pressure far below that recorded before stimulation.

The initial pressure with the bladder empty was 12·3 cm., and no change was noted on stimulation. With fluid in the bladder the rise and the ensuing relaxation could be demonstrated at each volume until the bladder was filled. The most marked rises occurred with the bladder volume of average capacity, and became less marked as the organ was approaching the limits of its capacity. No fluid ever escaped from the urethra when this rise in pressure occurred. As the bladder became filled the relaxation increased and was most pronounced with 40 c.c. of fluid in the cavity; it then lowered the pressure 16·7 cm. below the pre-stimulation level.

Due to the pronounced irritability of the bladder a chart could not be prepared to show the volume increase on sympathetic stimulation at all of the different levels of constant pressure, but the readings obtained at some of the pressure constants gave satisfactory information concerning the result. One of these readings is shown in Graph B of fig. 7. At the constant pressure of 21 cm. of water the bladder held 17·5 c.c. at equilibrium. Stimulation of the sympathetics effected no initial expulsion of fluid, but there at once occurred a rapid inflow of water to the bladder which continued until 22·4 c.c. had been added and the bladder volume increased to 39·8 c.c. On stimulation of the sympathetics the bladder volume was more then doubled.

This experiment demonstrates the power of the sympathetics over the automatic bladder. The initial rise undoubtedly represents a contraction of a portion of the bladder musculature; Elliott states that the sympathetics in the cat supply motor fibres to an area around the urethra. The contraction is more active than it is in the normal animal. The paralysed muscle is so irritable to stretch that it may augment the contraction of an isolated area. The diminution of pressure is also increased in these preparations. The pressure in the resting bladder is abnormally high, and the fall with relaxation lowers the pressure to a level that might be obtained on stimulation of the sympathetics in the normal cat. When the pressure is held constant, the volume may be doubled by sympathetic stimulation. Since it must not only expel fluid, but also cope with the inhibitory powers of the intact sympathetics, the bladder following parasympathectomy has to work against a double burden.

THE EFFECT OF SYMPATHECTOMY UPON THE AUTOMATIC BLADDER.

Testing the effect of sympathectomy upon the automatic bladder produced by previous parasympathectomy was the final aim of these

experiments. Considerable difficulty was encountered in maintaining the cats in good condition for the final operation. The findings are those which would be expected from the results already reported in this paper.

A re-examination of fig. 6 again emphasizes the effects of the previously discussed unilateral and bilateral parasympathectomy. Automatic micturition was established on a reflex capacity practically equal to that of the normal bladder. The abdominal sympathetic chains were removed and the next reading made four days later. The

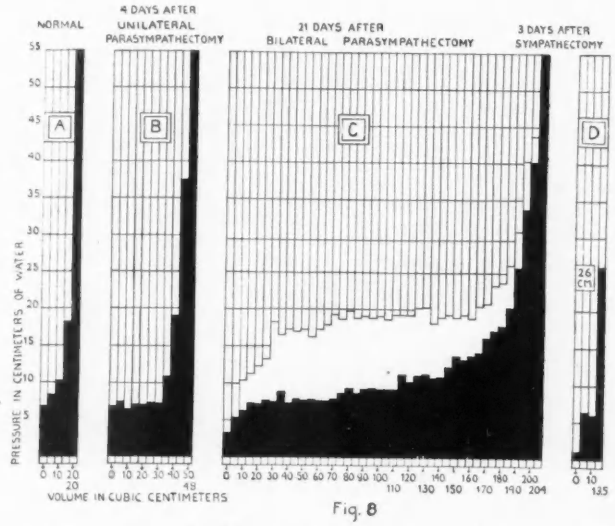

Fig. 8

FIG. 8.—This figure shows the changes in bladder volume and pressure after unilateral and bilateral section of the parasympathetic fibres and subsequent removal of the abdominal sympathetic chains. The white area in diagram C indicates the extent of the waves of vesical contraction after fluid had been introduced and the observer was waiting for the lowest possible reading.

reflex capacity was reduced from 47·5 c.c. to 25 c.c. (Graph F, fig. 6). The sphincter of the automatic bladder relaxed at 47·5 cm. and after sympathectomy at 41 cm. of pressure. When the bladder was being filled the pressure readings were lower than previously and similar to those already described after sympathetic section. With the viscus empty there was an initial low pressure which thereafter rose by a series of steps with the increasing volume, and exhibited no faculty for holding the ranges of volume at the same pressure. This ability had been retained after the parasympathetics were cut.

Lumbar sympathectomy had its most marked effect upon the large bladder, and this moreover was true even when the large volume was absent in the normal animal, but was produced by nerve injury. This is demonstrated in fig. 8. The normal bladder of this cat had an extremely small volume for reflex micturition (Graph A) : it emptied on 20 c.c. During the introduction of the increments of fluid, the pressure rose by a series of steps, the sympathetic nervous system normally exerting little control over this bladder. Four days after unilateral section of the parasympathetics, the reflex capacity had increased to 48 c.c. (Graph B). The parasympathetic fibres were then sectioned on the other side. Twenty days later the bladder was large and held 204 c.c. before fluid escaped from the urethra (Graph C). There was no infection of the viscus, but no decrease in reflex volume had occurred nor had reflex micturition developed. Within two weeks after the parasympathetics are cut, the bladder of the cat usually functions automatically.

The muscle was very irritable to stretch. The light area in Graph C of fig. 8 records the height of the contraction waves which occurred after the inflow of water had been stopped and the observer was waiting for the lowest pressure reading. The large volume of fluid was held at low pressures, and when the bladder was filled the pressure rose slowly by a series of steps, demonstrating an actual stretch of the elastic wall. As the bladder became distended, the spontaneous waves decreased in amplitude. At 204 c.c. fluid escaped from the urethra, but the bladder did not empty. Although the muscle of this bladder reacted forcefully to stretch, the viscus remained large and had not developed reflex micturition.

The abdominal sympathetic chains were then cut and the next reading taken three days later (Graph D). A dramatic change had occurred; palpation revealed that the bladder no longer lay in the abdomen, but in the pelvis. At this time its reflex capacity was 13·5 c.c., and the sphincter relaxed at 26 cm. The reflex volume was now less than in the normal cat. The bladder wall was still quite irritable to stretch, but not as much so as before the operation. Within three days the bladder capacity had decreased to one-fifteenth.

After sympathectomy there was a great improvement in the activity of the gastro-intestinal tract. Peristalsis of the large bowel became active again, and no longer was there an accumulation of fæces. The anal sphincter was less relaxed and eversion of the rectal mucosa less marked. Nevertheless, the reflex bladder in itself presented an obstacle to preserva-

tion of the cats, for they remained wet much of the time. They seldom could be kept in good condition for more than a few weeks.

Better chronic results were obtained in the few cases in which the internal pudendal nerves were spared, and the cats retained some control over micturition. Readings revealed that the bladder musculature reacted abnormally; the pressure readings were high, and the muscle was hyper-irritable to stretch. Following the operation the reflex volume was greatly increased and then became slightly less than normal. Under such conditions the reflex volume was decreased by sympathectomy and maintained its small size for months.

Discussion.

The bladder differs from an elastic non-viable sphere in its ability to hold varying quantities of fluid at approximately the same pressure; this ability is a function of the smooth muscle within its walls and is dependent also upon the intact innervation of the muscle. As has been shown in this paper, the accommodation is affected seriously by the cutting of the sympathetic nerve supply. After the death of the animal the smooth muscle remains viable for hours, and during this period the ability to hold increasing amounts of fluid at the same pressure is much less marked than in the live preparation; with the passage of time great diminution in this capacity is noted.

MacWilliams (1902), Osborne (1909) and Kesson (1913) have written of the elasticity of cavities formed for the most part of smooth muscle. MacWilliams studied the arterial wall during relaxation and in the state of post-mortem contraction. Osborne considered the elasticity of balloons and hollow viscera, including the bladder, while Kesson made observations upon the bladder. Flexner, Clark and Weed (1932) investigated the elasticity of the dural sac. The physics of elasticity in tensile membranes and particularly those of the living organs of the body becomes a complicated subject, but a graph showing our own observations (fig. 3) illustrates phenomena which help in understanding the activity of the bladder wall. Although manufactured rubber balloons were also examined, their properties differ so markedly from those of the bladder that discussion of the results would be unprofitable.

The irritability of the bladder is increased through its sympathetic innervation. This is evidenced by the increase in pressure which immediately follows stimulation, and by the decrease in irritability on section of the fibres. Sympathetic stimuli inhibit the tone of the muscle, permitting it to hold more fluid as well as varying quantities of fluid at approximately the same pressure. After sympathectomy the reflex

volume decreases, and with the addition of increments of fluid the pressure rises by a series of steps. Moreover, the recorded pressures in the bladder are lower than normal and the emptying mechanism appears to be more efficient. There are two opposing forces acting on the bladder through the medium of sympathetic stimuli. One produces a contraction of smooth muscle fibres at the base of the bladder and a slight rise in pressure, the other an inhibition of the detrusor muscle.

We have so far refrained from discussing the sympathetics in their relation to the sphincters. Our own experiments give only slight information concerning sphincter activity and at most record the pressure within the bladder at the time fluid escapes from the urethra. Moreover, we agree with the opinion of Denny-Brown and Robertson that the sphincters have little individual activity separate from that of the vesical musculature; the activity of the sphincters is related inversely to the activity of the detrusor muscle. When the tone of the bladder muscle is high, the tone of the sphincters is low : the reverse is also true. If the bladder muscle contracts forcefully, the sphincters relax and micturition always begins as an active and sustained contraction of the bladder musculature. Voluntary delay of micturition is effected largely through an inhibition of the contraction of the detrusor muscle, although it is also possible to increase the contraction of the external sphincter voluntarily. Often after sympathectomy little change was observed in the pressure at which the sphincter relaxed. In most instances, if a determination was made immediately after removal of the sympathetics, a decrease was noticed in this pressure. After a period of several days the pressure returned to its former height or was even higher.

Recently some doubt has been raised as to the part played by the sympathetics in the voluntary inhibition of micturition in man. This function may of course be considered either an active inhibition through the sympathetics or a decrease of the normal activity of the parasympathetics. Denny-Brown and Robertson (1933 A) demonstrated in normal man active inhibition of the waves of bladder contraction by an effort of the will. In individuals with complete section of the parasympathetics, but with the sympathetics intact, they maintained that this cerebral control was lost (1933, B). They believe, therefore, that cerebral inhibition of micturition is effected through the agency of the parasympathetics. This, of course, is possible, but the work reported here reveals such a marked decrease in bladder volume for reflex micturition following sympathectomy that it seems rather evident that all the inhibition of bladder function is mediated through the sympathetics.

Whether this is actually true for voluntary control will be a problem for further study.

Learmonth reported that patients notice a transitory frequency after section of the sympathetics. The present experiments demonstrating a marked decrease in bladder capacity after sympathectomy make one conjecture concerning the subjective results in terms of frequency. Normal voluntary micturition usually is initiated before the bladder has reached the limits of its capacity, whereas reflex micturition under anæsthesia is effective only when the bladder is filled completely. It is probably rare in man that the bladder is ever completely filled. Under such conditions a great change in bladder capacity might be noticed during the period when the reflex volume was decreasing, and would no longer be observed when the bladder became fixed at a constant lower capacity. After sympathectomy the pressure rises more rapidly when the bladder is filled, and this may be appreciated as urgency.

The authors are able to give little specific information concerning the improvement in function of the automatic bladder after sympathectomy. It may be said that the extremely irritable muscle of the automatic bladder is inefficient, and that the energy is utilized in holding the volume at a constant high pressure. The decrease in irritability and in intravesical pressure after sympathectomy may increase its efficiency. When the emptying mechanism is weak, a small volume may be expelled more easily than a large one. The bladder remained at a decreased volume following sympathectomy. One thing is clear: a bladder of initial large size will show a great diminution in reflex volume after sympathectomy. This is true whether the large volume is normal or dependent upon a lesion of the parasympathetics.

The sympathetics are in no way essential to normal micturition. In certain mammals they have developed an inhibitory control over the detrusor muscle which enables the animal to increase the interval between micturitions by enlarging the bladder volume. This advantage becomes a liability if the parasympathetic innervation is damaged as the inhibitory power renders emptying more difficult. If the sympathetics are then cut to make expulsion of urine more efficient, care should be taken to plan an operation which would prevent the regeneration of the fibres.

Summary.

Stimulation of the sympathetic fibres to the urinary bladder causes a quick rise of intravesical pressure followed by a slow fall to a point below the reading before stimulation. If the pressure is maintained at

a constant level and the sympathetics stimulated, a small amount of fluid first leaves the bladder and then a greater quantity enters the viscus, so that the bladder holds more than it did before the stimulation occurred. The results of stimulation are much more striking if the parasympathetics to the bladder have been sectioned a few days previous to the experiment.

After section of the sympathetics to the bladder, the viscus holds fluid at lower pressure than normally and loses the ability to hold varying quantities at approximately the same pressure. The muscle is less irritable, but the emptying reflex is somewhat more forceful than before. The quantity of fluid required for reflex micturition falls steadily during the first few days after sympathectomy. The decrease in volume after sympathectomy is greatest in bladders of large initial capacity.

After unilateral section of the parasympathetics, the function of the bladder musculature is impaired. When the parasympathetics are cut bilaterally, fluid is held at a pressure higher than that before operation and the muscle is extremely irritable. For the first few days after parasympathetic injury, the bladder has an increased capacity, but this falls somewhat lower than that of the normal when automatic micturition begins.

Removal of the sympathetic chains under these conditions of automatic micturition produces the same changes that have been recorded for this operation upon the normal animal. These are indications that the function of the automatic bladder is improved by section of the sympathetics.

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PLATE XII.

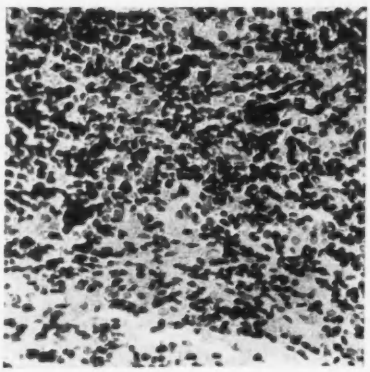

FIG. 1.—Myeloma showing an area of undifferentiated cells. (Case 1.)

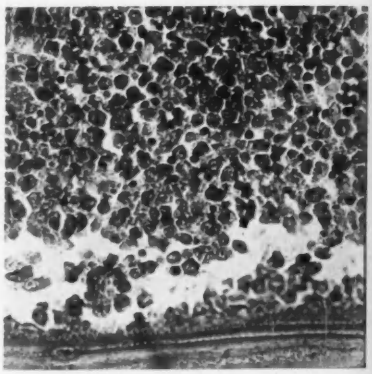

FIG. 2.—Myeloma. In this field the tumour cells resemble myelocytes. (Case 1.)

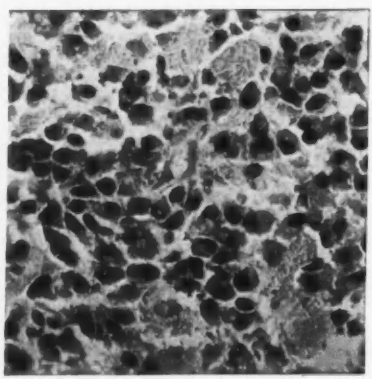

FIG. 3.—Plasma cell myeloma. (Case 2.)

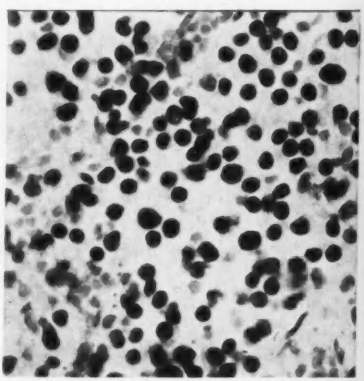

FIG. 4.—Plasma cell myeloma. (Case 4.)

To illustrate paper by Peter G. Denker and Samuel Brock.

THE GENERALIZED AND VERTEBRAL FORMS OF MYELOMA: THEIR CEREBRAL AND SPINAL COMPLICATIONS.[1]

BY PETER G. DENKER, M.D., AND SAMUEL BROCK, M.D.
New York, N.Y.[2]

MYELOMA may be regarded as a malignant tumour of bone-marrow arising either from a single-cell type, the plasma cell, or perhaps from a number of different bone-marrow elements. Depending upon the type cell—(1) plasmocytomas, (2) erythroblastomas, (3) myelocytomas, and (4) lymphocytomas have been differentiated in the myeloma group (Ewing [1]).

There is still a good deal of difference of opinion concerning the pathogenesis of these growths. Most pathologists regard either the plasma cells or the myeloblasts of the bone-marrow as the original cells of the growth. Others, including Christian [2], believe that the type cell is a transitional form, neither a plasma cell nor a myelocyte. In view of the almost constant bone resorption so characteristic of this tumour, the osteoblast has even been thought to be the type cell (Williams [3]). A very different conception of myeloma has been advocated by Witzleben [4], who regards it as a systemic disease of the blood-forming organs, closely allied to the leukemias, but aleukemic in nature, with predominant participation of the bone-marrow and the occasional involvement of other hematopoietic tissue. Lubarsch [5] believes that the myelomas belong to the group of hyperplastic, and not to the truly neoplastic diseases. An unusual case reported by Jackson, Parker and Bethea [6] is interesting in this connection. They describe a patient with a plasmocytoma of the tonsil removed eight years before generalized bone involvement could be detected. During the seven quiescent years "the process was spreading through the lymphoid system, as was proved by successive lymph node involvement, and eventually bone lesions characteristic of multiple myeloma made their appearance."

[1] Read by title at the Sixtieth Annual Meeting of the American Neurological Association, June 4, 1934.

[2] From the Neurological Service of Bellevue Hospital (New York), Dr. Foster Kennedy, Director.

The histology of the removed lymph nodes and of the bone tumours at autopsy was identical, i.e. plasma cell myeloma. These authors believe that the plasma cell tumour arose in the tonsil and spread through the lymphatic system, finally to enter the bone-marrow. They classify the plasma cell myeloma among the malignant lymphomata, rather than with the true bone-marrow tumours.

The disease is rare. Symmers and Vance [7] found only three cases in 4,000 successive autopsies at Bellevue Hospital, New York City. Four instances occurred in 9,000 consecutive autopsies at the Johns Hopkins Hospital, Baltimore.

The flat, short bones, viz., the ribs, sternum, scapulæ, skull and vertebræ, are especially involved. Soft grey or reddish grey masses start in the marrow, grow outward and replace the cortex of the bones. Secondary growths may appear in the liver, spleen, kidneys, lung and sex glands.

Myeloma occurs in the later period of life; 80 per cent. of Geschickter and Copeland's [8] series was between the ages of 40 and 70, with the greatest incidence at 55 years. Only five cases were found in people under 35, and of these two were not proven microscopically. It occurs twice as often in males as in females. In almost all cases there are multiple tumours. Pathological fracture of a rib or vertebra is a frequent late occurrence: in no other type of bone tumour does pathological fracture occur so frequently (62 per cent. of all cases). Bence-Jones bodies were found in the urine in 65 per cent. of Geschickter and Copeland's series, and in 80 per cent. of Magnus-Levy's [9] cases. The exact nature of these bodies, which precipitate between 50° and 60° C., only to disappear on further heating to 90° to 100° C., is not definitely known. They are not found exclusively in cases of myeloma, but have been reported in many diseases in which the bone-marrow is involved A possible relationship between this peculiar albumosuria and the blood proteins is suggested by the hyperproteinæmia found in some cases by Magnus-Levy and Freund [10]. They point out that this is not due to Bence-Jones bodies, however, but possibly to some substance analogous to fibrin. Geschickter and Copeland [11] report a recent case in which the patient's plasma proteins were 12·3 per cent. as compared to an average normal of 6 to 7 per cent. In this connection, Paige [12] found an unusual amount of amyloid deposition in almost all the organs of her case. She thinks this significant and possibly related to the Bence-Jones bodies in the urine. Nephrosis, anæmia and a chronic low-grade fever are reported in many cases.

No definitely curative form of treatment for generalized myeloma is known. Craver and MacComb [13] report favourable results in five of a series of six cases by the use of Heublein's method of total body X-ray irradiation.

The prognosis in cases of myeloma is very grave. The average duration of life is two years, the longest duration of any proven case being five and one-half years.

Once the tumour has appeared in many bones, the diagnosis is easily made. The age-group (fifth and sixth decades), multiple involvement of the short flat bones of the trunk, pathological fracture of a rib, Bence-Jones bodies in urine, progressive anæmia, nephrosis and cachexia make a highly characteristic clinical picture.

As an example of the generalized form, the following recently observed case may be cited.

Case 1.—B.L. (B.I.H., No. 20450 and No. 45816), a girl, aged 15, was first admitted to the medical service of Beth Israel Hospital, New York (Dr. I. Held), on November 2, 1931.

The family history stated that a brother died at the age of 9 of diabetes mellitus. The past history was irrelevant.

Her present illness began in May, 1931, with a persistent pain in the left upper quadrant of the abdomen. Two months later she fell on her back which immediately became painful; a few hours later she vomited. Vomiting continued for one week and the pain in the back increased. For two weeks there was cessation of pain but she grew weaker rapidly and lost 20 lb. in weight. Seven weeks before admission she was removed to another hospital, her appendix and gall-bladder were removed. The surgeon felt nodules in the tail of the pancreas and enlarged lymph glands and spleen. She made a satisfactory post-operative recovery but continued to vomit once or twice a week. Two weeks before entry the pain in the back reappeared; at one time a sneeze produced such a severe exacerbation of pain that she fell to the floor in agony. Five days before admission constipation, headache and left-sided abdominal pain were complained of. Just before entrance she felt dizzy and vision became blurred. One hour later she suddenly lost consciousness and generalized convulsions set in which lasted four hours. She bit her tongue during the fit. After the movements ceased she sank into a deep stupor.

Examination showed a young girl in deep stupor, pale and dehydrated. Neurological examination revealed no abnormal signs, the eye-grounds were normal. No glandular or abdominal masses were found. There was a tachycardia of 140 and mild clubbing of the finger-tips; slight pretibial œdema was noted. After a number of hours the girl's consciousness began to return. There was definite abdominal tenderness. For the next weeks the patient complained of pains along the spine and in the lower ribs and long bones; a polydipsia was also noted. She gained 4 lb. in weight. For the first few days

the temperature ranged from 99° to 100·4° F.; the pulse from 100 to 148; the respirations from 22 to 26. Her blood-pressure was raised at first, the systolic ranging from 158 to 184 mm. Hg, the diastolic from 112 to 140: the blood-pressure reached normal levels after a few days. A tachycardia of 96 to 116, an increased respiratory rate of 24, and an irregular temperature range of 99 to 101 persisted week after week. Her weight was 106½ lb.

The spinal fluid examination revealed entirely normal findings.

X-ray report was as follows: "Diffusely scattered through the skull, pelvis, ribs and in the diaphyseal ends of the fibulæ, the humerus, radius, in the acromion process of the scapula, and the acromial ends of the clavicles are numerous, small, circular, sharply-defined areas of osteolysis which appear to be medullary in origin and to involve the flat bones more than the long bones. The lesion in the long bones is located for the most part in the cancellous ends with the exception of the humerus where several foci are present in the mid-shaft on both sides but probably in the cancellated tissue. There is no expansion of bone, no periosteal reaction and no bowing or bending of the bones. The lesions show a tendency to confluence." Examination of the gastro-intestinal tract showed no abnormality.

Electrocardiographic study showed a sinus tachycardia.

Examination of the blood: In the first two weeks of her hospital stay the red blood-counts ranged from 3,300,000 to 3,510,000 with hæmoglobin estimations of 56 to 67 per cent.; the white blood-counts ranged from 7,100 to 19,200 with an average of 13,000; the differential count averaged: polynuclears 70 per cent.; mononuclears 30 per cent. In the latter weeks the red cells numbered 2,850,000 to 3,850,000, with hæmoglobin at 51 per cent. The previous leucocytosis gave way to a leucopenia ranging from 4,800 to 7,000 cells with polynuclears 42 per cent.; mononuclears 58 per cent. Four sedimentation rates averaged 63 per cent. Blood chemistry CO_2: 74·5 per cent.; glucose averaged 100 mgm. on three tests; sugar tolerance curves were normal. The non-protein nitrogen averaged 44 mgm. on three tests; calcium 9·2 to 9·8 mgm.; phosphates 3·2 mgm.

Nine examinations of urine made between November 2 and November 6 showed faint traces of albumin on three occasions. Bence-Jones bodies were sought on three occasions in vain.

The basal metabolism was minus 7 per cent.

Because of the history of a "nodular pancreas" felt at operation and the convulsions, adenoma of the pancreas was believed to be present, but blood sugar studies failed to substantiate this diagnosis. Moreover, the X-ray findings pointed to diffuse bony disease. The diagnosis on discharge, December 8, 1931, was generalized xanthomatosis.

She was readmitted to the hospital on January 10, 1932. Generalized malaise, headache, polydipsia and vomiting had continued. On January 6, 1932, she complained of painful gums; two days later she fainted and was stuporous for a number of hours; then she became overactive, danced about and sang while in bed. Convulsive seizures lasting one and a half hours

occurred on the day before admission. At this time she was pale, greatly excited and incoherent (post-epileptic state); this agitation alternated with periods of semi-stupor. A small exostosis was found in the right frontal region. The temperature varied from 99° to 100° F., the pulse-rate from 106 to 132 and the respirations varied from 18 to 24. The blood-pressure on admission was S.168/D.130; later S.130/D.90. Her weight was 97½ lb. Neurological examination was again negative. Glucose injections were of no benefit. In two days she became coherent, quiet and comfortable. Within ten days dizziness, headache and vomiting reappeared. During this period her blood-pressure was raised S.156/D.116. X-ray therapy was given to the skull; despite thirteen treatments there was no regression of the pathological process.

Early in February, 1932, the ribs felt nodular and a lower thoracic kyphosis appeared. In March, 1932, the audiogram showed slight bilateral diminution in hearing, more marked on the right. In the next few months she went rapidly downhill. Pains in the head, teeth, ribs and spine were complained of. The lower thoracic kyphosis became more marked. She vomited occasionally. A sacral bed-sore appeared. In March the spleen was felt. The tachycardia and moderate hypertension continued. Œdema began late in June, especially over the ankles, it spread to include the face and became generalized. She died on July 24, 1932, in a state of advanced cachexia.

During the period of her second stay in the hospital the spinal fluid showed an increased pressure of 205 mm. and increased protein to 130 mgm.

X-ray examination: "There has been a considerable increase in the number and size of the areas of osteolysis in the various bones previously mentioned. In the ribs are multiple lesions with expansion of their cartilaginous ends. The vertebræ show diffuse involvement. The upper ends of both humeri and the ends of the clavicles contain multiple foci which have a tendency to coalesce. There is an area of osteoclasis in the region of a lower molar tooth in the right lower jaw. There are no changes in the left half of the mandible. There is irregular atrophy with lacunar destruction of the posterior portion of the right os calcis; there are similar lesions at the end of the epiphysis of the right tibia in juxtaposition to the fused epiphyseal line. There is a slight perforation of the cortex at the posterior surface of the lower end of the tibia. The proximal end of the metatarsal bone of the big toe shows a linear area of irregular atrophy. There is a similar distribution of atrophy in the distal ends of the second to the fifth metatarsal bones and in the proximal end of the proximal phalanx of the big toe."

Six blood-counts revealed a progressive anæmia, the counts ranging from 3,300,000 to 1,910,000; anisocytosis, poikilocytosis, polychromatophilia and toxic degeneration of neutrophils were noted. The hæmoglobin sank from 49 to 33 per cent. The reticulocyte count was 1·2 per cent. A white cell count of 6,400 with an average count of 71 per cent. polymorphonuclears and 29 per cent. mononuclears was found. Coagulation time was four minutes on one and three minutes on another occasion. The blood phosphatose was increased.

Estimation of the blood proteins gave the following figures:—

	6.2.32	11.4.32	18.5.32	23.6.32	6.7.32
Total protein ..	5·50	4·68	4·28	4·20	4·25
Albumin	2·81	2·95	1·56	1·75	1·93
Globulin	2·69	1·73	2·72	2·45	2·32
Albumin-globulin ratio	1·0	1·7	0·57	0·71	0·85

Twenty-one urine examinations showed traces of albumin; a number showed hyaline and granular casts; the specific gravity remained low (1005 to 1012). Bence-Jones bodies were again sought for in vain on different occasions. On January 28, 1932, the xylose test showed definite impairment of renal function, the maximal concentration being 0·65 per cent. (normal 2·5 per cent). On February 4 doubly refractive bodies were found in the urine.

A biopsy from a rib was made. The consistency of the rib was fairly normal. Its cut surfaces had some brown irregular areas. Microscopically the picture was that of a myeloma showing a rather indifferent small type of cell, the average size being 5 to 6 micra (Plate XII, fig. 1). The cytoplasm was indistinct, the nuclei were dense and without regular structure. No reticulum was seen. The outlines between the tumour and the surrounding bone marrow were indistinct, there were very few places only where a fine layer of connective tissue separated the myeloma from normal bone marrow. There were many thin-walled capillaries. An occasional area was occupied by more highly differentiated cells resembling myelocytes (fig. 2).

There was an incomplete autopsy. Some material was available from the spleen, kidney, pancreas, liver, and intestine. The kidney and liver contained more or less well outlined areas corresponding in structure to the myeloma described above. In addition many lime deposits were seen in the kidneys: these were attributed to widespread destruction of bone throughout the body. The pancreas revealed a most surprising picture. Grossly it appeared light yellow and unusually firm. Microscopical sections consisted mainly of dense connective tissue and contained only a small amount of pancreatic parenchyma, the condition of which could not be judged on account of post-mortem change. This, unfortunately, applied to the islands as well. Many of the pancreatic ducts were wide and contained homogeneous, partly broken-up masses. These did not consist of lime since they could be dissolved in inorganic acids and did not take the hæmatoxylin stain. One of the concretions was examined chemically for cholesterol but none was found. Only a small amount of inflammatory infiltration was seen in the pancreas.

The final pathological diagnosis was: Multiple myeloma, myelomatous infiltration and lime deposits in the kidneys, myelomatous infiltration and severe fatty changes in the liver, severe atrophy and fibrosis of pancreas with concretions in the pancreatic ducts. (Dr. A. Plaut.)

Comment.—The unusual features of this case were the youth of the patient, the recurrent convulsions and the polydipsia. Among the laboratory findings, the marked involvement of the skull was of especial interest; in the post-mortem examination, the myelomatosis, the lime

deposits in the kidney and the atrophy and fibrosis of the pancreas with concretions of the ducts. The convulsions were readily attributed to the cerebral effects of the countless bony tumours in the skull. The polydipsia was regarded as part of a diabetes insipidus, due to bony invasion of the basilar parts of the skull with secondary effects on the pituitary gland or on the structures of the floor of the third ventricle. Diabetes insipidus has been described by Aronsohn [14] in a case of multiple myeloma due to such basilar involvement. This author discussed the cause of these secondary effects—whether induced by toxins, produced by pressure of the growth or by impairment of vascular supply. Direct pressure did not seem to play as important a part as in the vertebral type to be next described.

Neurological signs are found in 40 per cent. of cases of myeloma. As will be seen, paraplegia due to compression of the spinal cord is not uncommon. Signs of medullary disease, such as glossoplegia, dysphagia and alteration of voice due to paralysis of laryngeal muscles have been noted. Diplopia, Horner's syndrome, evidence of spinal root involvement and herpes have also been reported (Geschickter and Copeland [8]).

Since its original description, myeloma has always been regarded as a tumour of multiple incidence, hence the term "multiple myeloma." Ewing [1] does not even refer to their isolated occurrence. In a most exhaustive study of 425 cases reported in the literature, Geschickter and Copeland [8] conclude that "exceptions are so rare that the statement that myeloma is always multiple and always involves the trunk, is practically vindicated." Magnus-Levy [9] likewise is not convinced that any of the reported rare examples of solitary myeloma were truly proven. He points out that most of the cases were not autopsied, not followed long enough after the original diagnosis was made, nor thoroughly studied, especially by X-rays.

In a thorough search of the literature only three undoubtedly proven cases are found. These are: The rapidly fatal case of Cabot [15]—a man of 32 with a myeloma of the fourth thoracic vertebra; the lesion was found to be limited to this site at autopsy. The case of Geschickter [16]—a man of 45 with a plasma cell myeloma of the femur, proven by biopsy; X-rays of all other bones were negative and no Bence-Jones bodies were found. The case of Harding and Kimball [17], the myeloma being found in the femur of a man of 65; autopsy revealed only the one lesion.

Many of these "solitary" myelomas begin in a vertebral body and

announce their presence by signs of compression of the cord. Recent reports by Wakely [18], Jacox and Kahn [19], and Klemme [20], and our own experiences show that this vertebral form of the disease is not so rare. While the separation of this group from the pathological viewpoint may be an artificial one, it would seem justifiable on clinical grounds because for a considerable period of time the growth is confined to the vertebral and extradural tissues. Moreover, the patient may die before the growths become widespread. In this variety the typical picture presented is that of a man or woman in the fifth or sixth decade who rapidly develops the signs of a transverse spinal lesion with manometric block. The thoracic cord is usually the site of the cord compression; there is focal spinal tenderness. X-ray of the spine may be negative or show destruction of the body of the vertebra. No primary focus of malignancy can be demonstrated elsewhere. Laminectomy reveals a grey or reddish grey extradural mass either pushing the cord backward or encircling it. The growth can be traced frequently to the diseased vertebral body. Removal of the extradural mass decompresses the cord and great improvement follows the operation. Our third patient was relieved for two years before recurrence and pathological fracture occurred; the second patient, bedridden with a paraplegia, was enabled to get up and walk about. He is now transacting his daily business, nine months after operation. Jacox and Kahn [19] describe beneficial results from laminectomy in two cases and relief of root pains by the subsequent use of X-ray therapy. Klemme [20] also reports favourable results after laminectomy in four of his five cases. However, the ultimate outlook is very grave; a pathological fracture is the constant menace, together with the reappearance of the disease in other bones, leading to the signs noted under the generalized form of the disease, and finally death.

As examples of the vertebral form of myeloma, the following three cases are cited.

Case 2.—H. McC. (B.H. Neur. No. 679), a man aged 48, a mechanic by occupation, was admitted to the neurological service of Bellevue Hospital, on June 29, 1933.

The family and past history were irrelevant. He was a heavy drinker of alcohol for many years.

His present illness had a gradual onset, nine months before admission, with localized pains in the front of his right chest; these later radiated to the interscapular region posteriorly. The pains were aggravated by deep inspiration, sneezing or coughing, and became more severe; very recently they appeared bilaterally. For about two weeks before admission he also noticed

weakness and unsteadiness in his lower extremities, especially when he descended the stairs. His legs often felt numb as if "they were asleep," at other times as if he were walking "on something soft." There were no bladder symptoms nor any pains or weakness in his upper extremities. He lost about 10 lb. in weight since the onset of his illness.

Examination revealed a poorly nourished middle-aged man, not acutely ill. He was co-operative and of average intelligence. A bilateral hydrocele and a slightly enlarged prostate of regular normal consistency were noted. The spinous processes of the third and fourth thoracic vertebræ were slightly prominent and tender. The blood-pressure was S.120 D.80.

Neurological examination: The cranial nerves were normal. The gait was somewhat spastic. There was a marked weakness of both lower extremities, the right being weaker than the left. There was no atrophy, fibrillation or ataxia. Sensory examination revealed a loss of pain, light touch, and temperature sense below the fourth thoracic dermatome on the right and the seventh thoracic on the left; the peri-anal region was included in this impairment. Position sense was normal in the toes; vibration sense was moderately diminished up to the ankles. The deep reflexes were normal in the upper extremities. Both knee-jerks were overactive. An unsustained bilateral ankle clonus and a bilateral Babinski toe sign were found. The abdominal and cremasteric reflexes were absent.

Immediately after lumbar puncture increased weakness of the lower extremities with complete retention of urine developed. He became bedridden. The sensory level at thoracic-4 was accentuated with more marked hypalgesia below this level.

Spinal fluid examination disclosed a xanthochromic fluid under a pressure of 80 mm.; complete manometric block to jugular compression was present, but after cisternal puncture normal fluctuations to compression were found. The spinal fluid showed two cells with a total protein of 300 mgm.: the Wassermann reaction was negative.

X-ray of the spine showed destruction of the body of the fourth dorsal vertebra with some lateral buckling; no evidence of new bone formation was seen. X-rays of all other long bones, including chest, sternum and skull, were negative.

Examination of blood: hæmoglobin 75 per cent.; red blood cells 3,900,000; white blood cells 11,000: polynuclears 70 per cent.; lymphocytes 26 per cent.; transitionals 2 per cent.; eosinophiles 2 per cent. Non-protein nitrogen 30 mgm., blood sugar 77 mgm. per 100 c.c. of blood.

The analysis of the urine was negative, though repeatedly examined for Bence-Jones bodies, but none were found.

On July 6, 1933, Dr. D. Klenke performed a laminectomy (second, third and fourth thoracic segments). A large tumour mass was found invading the body of the fourth thoracic vertebra. The tumour also involved the posterior right half of the arch. The dural sac was bent backward by the tumour at the level of the fourth thoracic vertebra. The growth was removed extra-

durally, completely relieving the angulation and restoring normal pulsations in the cord. It was felt that the tumour had arisen from the bone itself and could, therefore, not be completely removed, although practically all of the intra-spinal portion was excised. The tissue proved to be a typical plasma cell myeloma (Dr. Douglas Symmers) (fig. 3).

The post-operative course was uneventful. There was gradual improvement and return of strength in the lower extremities and complete relief of pain. Deep X-ray therapy was immediately begun. At the time of discharge from the hospital on December 27, 1933, he was able to walk up and down the wards without support, except for a brace applied to his back. By the end of January, 1934, he had finished two courses of radiation therapy of ten treatments each. He was walking well except for some slight spasticity. There were no bladder disturbances. There was no further loss of weight. He still showed overactive knee and ankle jerks. His plantar reflexes were equivocal. A slight abdominal flicker was obtained on the right, none on the left. The sensory changes had completely disappeared. He was examined again on April 13, 1934. His gait was a little spastic and insecure; no Romberg sign was elicited. The knee and ankle jerks were still over-active. There was a left Babinski toe sign. The abdominal reflexes were absent. A level was found at thoracic 6, below which there was very slight hypæsthesia and hypalgesia; temperature, position and joint and vibratory senses were intact. He noted an occasional trifling urinary incontinence.

X-rays of all other long bones, chest, sternum, pelvis and skull continued to be negative.

Case 3.—M. M. (B. H. Neur. No. J 182), a mulatto housewife, aged 48, was first admitted to the neurological service of Bellevue Hospital on March 8, 1928.

The family and past history were irrelevant.

Her present illness began two months before entry with gradual weakness in the lower extremities. The weakness was first noticed in the left knee; later the left ankle would turn in as she walked, causing her to trip. The disability became worse, and one week before admission power in the right leg also became affected in a similar way. She also complained of numbness and coldness in the legs. There were frequent attacks of severe pain beginning in the lumbar region and radiating down both thighs to the calves. There were no bladder symptoms.

Examination revealed a middle-aged mulatto woman in a good state of nutrition. There was a moderate amount of tenderness over the second thoracic vertebra. The blood-pressure was S. 178/D. 110.

Neurological examination.—The cranial nerves were normal. There was great weakness of both legs, more marked on the left. The knee-jerks were overactive, the left being greater than the right; a left patellar clonus was elicited. Both ankle-jerks were absent. There was a definite Babinski sign on the right; the left plantar response was equivocal. The abdomical reflexes were absent. Motor power and all the reflexes in the upper extremities were

normal. There was a defect to all forms of sensation, except position sense, which was intact up to the fifth thoracic dermatome; the peri-anal region was also involved

Spinal fluid examination disclosed a clear, colourless fluid with sixteen cells per c.mm.; globulin was much increased, Wassermann negative, colloidal gold curve 4433221000. The pressure was 145 mm.; there was a complete block to jugular compression.

X-rays of the spine showed an erosion of the third, fourth and fifth thoracic vertebræ; the body of the fifth was completely compressed. The inter-vertebral spaces between the third, fourth, fifth and sixth thoracic vertebræ were entirely obliterated. X-rays of the skull, the chest, ribs and all the long bones were negative.

The blood Wassermann was negative. Examination of the blood: hemoglobin 60 per cent., with 3,500,000 red blood cells; 7,800 white blood cells; 66 per cent. polynuclears; 30 per cent. lymphocytes and 4 per cent. basophiles.

Analysis of the urine was negative; repeated examinations of the urine for Bence-Jones bodies were negative.

Operation was performed on March 28, 1928 (Dr. Alfred S. Taylor). Laminectomy over the third, fourth, fifth and sixth thoracic vertebræ revealed thin, diseased bone infiltrated by an extradural tumour which compressed the spinal cord and encircled the dura. There was a fixed portion anteriorly and to the right. Most of the growth was removed in fragments. The tumour involved the body of the fifth thoracic vertebra, so that complete removal was impossible. At the end of the operation the dura pulsated normally with respiration.

The post-operative course was one of gradual improvement. Deep X-ray therapy was begun. In a few weeks the patient was able to get up out of bed and walk about the ward with back-brace and crutches. However, her level still persisted at the fourth thoracic dermatome. The neurological signs were essentially the same as on admission. She was discharged on July 18, 1928.

The sections of the tumour removed at operation showed a plasma cell myeloma—"tissue composed of closely packed cells with hyper-chromatic nuclei in which the chromatin is arranged radially in cart-wheel fashion. Some of the nuclei are eccentrically placed. The cytoplasm is pale blue in colour". (Dr. D. Symmers).

The patient improved so rapidly that within two months she was able to walk about and attend to all her duties unassisted. This improvement persisted until February, 1930. She noticed that her legs were getting progressively weaker, and at night her lower extremities would tend to "draw up spontaneously," so that whenever she wanted to turn over she would have to extend them vigorously. There had been no sphincter disturbances. Two weeks before readmission (March, 1930) she tripped in the street.

The neural status was essentially the same as on the first admission: bilateral spastic paraplegia with overactive reflexes and bilateral Babinski

toe signs, and sensory defects in all forms of sensation up to the fifth thoracic dermatome.

Lumbar puncture was again performed, but no fluid was obtained.

Since she had evidently a recurrence of the growth with resultant compression of the cord, laminectomy was performed April 7, 1930 (Dr. D. Klenke). The bodies of the fourth and fifth thoracic vertebræ were soft and mushy and evidently infiltrated by tumour. There was compression and angulation of the cord at this level, so that the entire dural sac was pushed sharply backward by the ventrally placed neoplasm, which extended from the third to the fifth thoracic vertebra. A definite degree of atrophy of the cord was present. As much of the growth as possible was removed.

Sections of the tissue at this time again revealed a plasma-cell myeloma (Dr. Douglas Symmers).

The patient improved greatly after the operation and deep X-ray therapy was again begun. She was able to walk the length of the ward unassisted. On November 12, 1930, there was a sudden onset of acute pain in her back at the level of the operative area with an instantaneous complete paralysis of both lower extremities. Examination showed a complete flaccid paraplegia of the lower extremities with absent deep reflexes and a level at the seventh thoracic dermatone, below which sensation was entirely lost. There was tenderness over the fifth thoracic vertebra. Complete retention of urine and fæces was present. X-rays now showed complete destruction of the fourth and fifth thoracic vertebral bodies. It was not felt that surgical intervention would be of any benefit; she was therefore placed in extension and given routine nursing care.

Repeated X-rays of all the long bones, skull and sternum at this time were negative. Search for Bence-Jones bodies in the urine was again unsuccessful. Her course was gradually downhill. She developed a cystitis, ran a low-grade fever for months, and was transferred to the Central Neurological Hospital, where she died on April 5, 1932.

Autopsy was performed by Dr. Vera Dolgopol. Severe erosion of the third, fourth and fifth thoracic vertebræ was found, as well as erosion of the tenth, eleventh and twelfth thoracic vertebræ. Soft pieces of tumour were found extending into the spinal canal between the softened bones. The spinal cord was atrophic in the upper thoracic segments at the region of the operation. The skull showed no thickening of the bone and no tumour masses could be found in it. Examination of the brain was essentially negative.

The heart was slightly dilated, especially the right ventricle, with intact valves and a somewhat flabby myocardium. The aorta showed atheromatosis. There was lobular pneumonia in the lower lobes of both lungs, with congestion of the bronchi.

Bones: A greyish soft tumour containing hæmorrhagic areas, 4 by 2 cm., was found at the chondral attachment of the left fifth rib. The vertebral parts of both fifth ribs were transformed into tumour tissue by direct extension from the vertebral focus. The right iliac bone crumbled easily: a blood-clot was

seen between the laminæ of the iliac bone. The spleen showed moderate congestion with hyperplasia of the pulp. The liver was essentially normal, except for one firm, grey nodule, 2·5 cm. in diameter, in the right lobe. The gall-bladder and pancreas were negative. The kidneys were normal, except for old arteriosclerotic infarcts and adherent capsules. A few retracted scars were seen in the cortex which were regarded as old healed infarcts. The rest of the genito-urinary tract was normal except for a chronic cystitis. The stomach and small intestines showed no pathological change. The colon revealed a pale, slightly indurated ulcerated area 2 cm. in diameter, at about the region of the splenic flexure. A small, firm, white nodule was found in the mesentery near the colonic ulcer.

The final pathological diagnosis was plasma-cell myeloma of the various bony tumours described, and a primary adenocarcinoma of the colon with metastasis to the mesentery and liver.

Case 4.—N. D. (No. 2980), a woman aged 64, was admitted to the medical service of St. Vincent's Hospital, Staten Island, N.Y. (Dr. Herbert A. Cochrane), on August 2, 1932, complaining of pain in the left lumbar region which began two months before admission. It was often sharp in character and radiated across the back and abdomen.

The family and past history were negative except for a left-sided nephrectomy performed in 1905.

The motor power in the lower extremities and control of the bladder and rectum were completely lost. Anæsthesia and analgesia were found below the twelfth thoracic dermatone. A diagnosis of a metastatic spinal tumour was made (September 23, 1932). One week later, Dr. C. C. Hare noted that the sensory level was unchanged, and that the tendon reflexes in the lower extremities were greatly diminished on the right and lost on the left; there was no response on plantar stimulation.

Spinal fluid examination revealed a clear, colourless fluid; manometric readings showed a complete block.

X-ray examination of the genito-urinary tract revealed hypertrophy of the right kidney; there was no evidence of intrathoracic lesion: the sacro-iliac joints were normal. The gastro-intestinal tract showed spasticity of the colon and probably a congenital transduodenal membrane. X-rays of the lower thoracic and lumbar vertebræ revealed spondylitis or possibly trophic disease.

Examination of the blood showed: Hæmoglobin 80 per cent.; red blood-cells 4,760,000; colour index 0·85; white blood-cells 12,000; polynuclears 83 per cent.; small lymphocytes 16 per cent.; large mononuclears 1 per cent.; some degree of anisocytosis was noted. Blood sugar ·097 per cent.; urea nitrogen 12·3 mg.; urea 26·3 mg.; uric acid 2·0 mg.; creatinin 1·7 mg.

A number of urine examinations showed a trace of albumin, occasional hyaline and granular casts and an occasional leucocyte and erythrocyte; there

was a pre-agonal acetonuria. Examination for Bence-Jones bodies was not carried out.

The patient died on October 2, 1932.

The autopsy was performed by Dr. M. Freund.

Microscopical study of the tumour disclosed the picture of a myeloma (fig. 2). The type cells were middle-sized, with large characteristic nuclei, some light, others dark by staining; an occasional cell contained hæmoglobin; dark nucleated red cells were seen. Another type of large cell resembled a megakaryocyte. The stroma of the tumour consisted of fine connective tissue fibres containing numerous capillaries, which were markedly distended. Hæmorrhagic foci were noted. Other sections revealed similar pictures with a larger number of megakaryocytes. Oxydase staining showed that these mononuclear cells were oxydase negative.

The spinal column, at the region of the eleventh thoracic vertebra, was prominent. On palpation, this vertebral body was replaced by soft tissue, which could be removed without any difficulty. The same changes were present in the fourth and fifth ribs on the left side near their vertebral ends. At the point where it passed the eleventh thoracic vertebra, the spinal cord was compressed.

The serosal surface of the bladder showed bluish discoloration; it was distended. The mucosa was dark bluish-red and necrotic. The submucosa was densely infiltrated with polynuclear leucocytes and plasma cells; the infiltration extended to the muscular coat.

The uterus was normal, except for a myofibroma the size of a hazel-nut on the right. The Fallopian tubes were normal. The ovaries were markedly fibrotic.

The cortex of the adrenal was poor in lipoid; the medulla was well developed.

The final pathological diagnosis was multiple myeloma, broncho-pneumonia, cystitis.

Comment.—The age incidence (53 years) of the foregoing three cases was the usual one. In all, the signs pointed to compression of the thoracic cord with manometric block. Bence-Jones bodies were not found in the urine in two of the cases. In two, the X-rays showed evidence of destruction of a vertebral body. In four of Klemme's five cases there were no X-ray changes; on the other hand, in one of the cases reported by Jacox and Kahn the destruction of the third lumbar vertebra finally became so complete as to lead to the disappearance of the vertebra. In the first case of the man still alive, we are dealing with a myeloma which is as yet solitary. In the second and third cases the myelomatous process was relatively circumscribed to vertebræ and adjacent ribs. The duration of the illness was well illustrated by the second and third cases—fiffy-two months in one, four months in the other. The terminal infections in the bladder and lung need no comment. The presence of an

associated adenocarcinoma of the colon with mesenteric and hepatic metastasis came as a complete surprise in the post-mortem of the second case.

The spinal signs in cases of myeloma are not always due to pressure from the neighbouring growth. Nonne [21] reported the case of a man aged 57 who was taken ill with severe pains in the neck and arms; muscle atrophy in the ulnar parts of the hands, miosis, priapism and tenderness on pressure of the lower cervical spine developed and pointed to a "cervical meningomyelitis." X-rays revealed rarefaction and shrinkage of the first thoracic vertebra. Cachexia set in rapidly and death occurred in two months. The vertebral lesion was a myeloma. Microscopical study showed no demonstrable cord lesion. Nonne believed that a toxic effect was produced on the cord by the neighbouring myeloma. Kreuzer [22] described multiple focal degenerations in the dorso-lateral white matter of the spinal cord, especially marked in the ninth and tenth thoracic segments, which he believed followed hæmorrhages. Since autopsy revealed a myeloma of the fourth and fifth thoracic vertebral bodies, this author concluded that the distant effects of the tumour on the cord could not be caused by mechanical pressure but were due to the action of the toxin.

Conclusion.—Four instances of myeloma are described with neurological complications. The first is an example of the generalized form of the disease. The other three illustrate the vertebral type in which the myeloma is circumscribed to vertebral and extradural tissues at the time of the rapid development of signs of spinal cord compression. The upper thoracic cord is usually the part involved. The patient is generally in the fifth or sixth decade of life. X-rays may show destruction of the diseased vertebra. Laminectomy reveals a reddish-grey extradural growth, removal of which is followed by great, if temporary, improvement. Deep X-ray therapy and the wearing of a back-brace are advised after laminectomy.

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EFFECTS OF EXPERIMENTAL LESIONS OF THE POSTERIOR COLUMNS IN *MACACUS RHESUS* MONKEYS.

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I.—Introduction.

Although it is generally assumed in textbooks on clinical neurology that the functions of the dorsal columns are well known, being essentially those concerned with the transmission of the more discriminative types of sensibilities, it is remarkable how few experiments have been performed in animals on the dorsal column system, especially in forms such as the monkey. To be sure, most of our knowledge concerning the physiopathology of the dorsal columns has been obtained from human cases. However, in such cases the lesions are usually not well circumscribed and not confined alone to the dorsal column system. In tabes, for example, there is usually an involvement of dorsal roots in addition to that of the dorsal columns, and in tumours or traumatic conditions the extent of the involvement is also generally greater than the posterior columns themselves. In other diseases involving the dorsal columns, such as multiple sclerosis, combined sclerosis and degenerative or other diseases, the pathological process is rarely, if ever, confined entirely to the dorsal columns, and it seemed of interest to us, therefore, to investigate experimentally the function of the dorsal column system as the first step in an analysis of the effects of lesions at various points in the sensory system.

Even when one reviews the experimental work performed by physiologists on the dorsal columns and the dorsal column nuclei in the medulla one finds very few uncomplicated cases where the experimental lesion was confined entirely to the dorsal columns or their nuclei. In addition, many of the earlier experiments were performed merely as acute experiments and little was learned concerning the ability of the animal to engage in its daily activity and of its ability to compensate for the loss of function of the dorsal column. In most of the earlier work unsatisfactory anatomical controls were reported, and in cases where more than gross anatomical reports weregiven in adequate

drawings were presented. On the other hand, much of the earlier work was concerned with the effects of lesions, or removal, of the dorsal columns in the thoracic region, not therefore involving the anterior limbs; whereas, we feel, that the most interesting result from a clinico-physiological standpoint is that following the lesion of the posterior column in the cervical cord, which involves, especially in the higher types of animals, both front and hind limbs.

It has been our purpose, therefore, to establish first of all the anatomical relationships of the dorsal columns and dorsal column nuclei. This is being reported at length elsewhere. On the basis of these anatomical findings, we have hoped to explain the symptomatology resulting from lesions at the different levels of the dorsal column system, particularly of the cervical region, and from lesions of the dorsal column nuclei. A large series of animals has been operated upon to obtain these results. All have been carefully controlled anatomically and the behaviour of the animals recorded by moving pictures at various acute stages up to the chronic stages of many months.

II.—Review of Literature.

Numerous early authors were concerned with the functions of the dorsal columns from the standpoint of conduction of various types of sensation. Bell [1], for example, believed that the dorsal columns conducted practically all forms of sensation to the brain, in contrast with the anterior columns which conducted motor impulses towards the spinal cord.

On the other hand, Bellinger [2] and others found no disturbances in sensation after cutting the dorsal columns, whereas Longet [3], Van Deen [4], Fodera [5], Magendie [6], and others supported Bell's general findings.

Brown-Séquard [7] found complete anæsthesia below the region in animals following lesions of the spinal cord in cases in which the dorsal spinal columns were spared. He explained the difference in his findings from those of Longet by the fact that in his experiments the grey substance remained intact. Brown-Séquard believed that the grey substance of the cord carried sensations and that when this was cut the anæsthesia occurred.

The work of Schiff (1857) [8, 9] determined opinions in neuro-physiology for many years. He believed that, in general, the dorsal column is the sensory path for various deep sensibilities. Since this is the main path, loss of the dorsal column cannot be compensated to any

great extent. He believed that section of the dorsal column causes a permanent loss of deep sensibilities, that the sense of position is only a function of the tactile sensibilities, and that the loss of sense of position following lesion of the dorsal columns is really due to or based upon the loss of touch and that the two are usually involved in the same degree. In his animals he stated as evidence of the loss of sense of position that the animals slide the feet along, especially if the floor is uneven. The dogs lift their feet to various abnormal degrees on running, sometimes too much and sometimes too little. Schiff maintained that the symptoms observed by him in the dog were essentially those described by Fritsch and Hitzig after removal of the cortical area described previously by Munk as the sensory sphere. Schiff compared the findings in his animals with those following cortical lesions and, based upon the similarity in symptomatology, postulated a course of the dorsal columns to the cortex. He thought that partial compensation occurs in the animals, for example a wider spreading of the toes which prevents the animal from turning the foot over with the dorsum downward, an occurrence observed in the early stages following the operations. Likewise, the animal could compensate to some extent by increasing the pressure of the foot on the ground on walking, thus allowing harder pressure to compensate to some extent for the deficiency of touch. Schiff considered that pain was conducted in the grey matter, whereas the white substance of the dorsal columns was considered as primarily concerned with the tactile stimuli.

Von Leyden (1863) [10] described symptoms in animals similar to those of Schiff and confirmed his work in the main points.

Ewald (1898) [11] removed about 7 cm. of the dorsal columns from the thoracic region of a dog and described, in addition to what he termed a motor ataxia in the hind limbs, a tactile and thermal anæsthesia in the animal below the lesion. The sense of pain did not appear to be diminished. The ataxia in the hind limbs improved greatly, and several months after the lesion, little, if any, abnormality in the sensory-motor sphere could be found. The touch and temperature loss, however, remained.

Türck [12] found a swaying gait and some anæsthesia distal to the lesion of the dorsal columns in lower animals such as the rabbit. This persisted only for a short time, and there was no marked cutaneous sensory loss.

Munk [13] developed his " Berührung " reflex as evidence of intact cortical representation. To elicit this reflex the animal was suspended

in the air by the neck and trunk with the legs hanging free and the eyes shielded. Light touch on a limb usually called forth a prompt moving of the limb away from the stimulus. This disappeared following lesions of the sensory sphere and also of the dorsal column system.

Bickel (1898) [14] removed a portion of the dorsal columns in the thoracic region of a dog, and reported a long-lasting sensory deficiency with ataxic symptoms in the hind limbs. The ataxia disappeared before the sensory loss. He believed that one of the main functions of the dorsal column was the conduction of "muscle sense." Pain and temperature were not lost.

Martinotti (1890) [15] found no disturbance of movement and sensation after section of the dorsal columns.

Borchert (1902) [16] reported the effects of lesions of the dorsal columns in thirteen dogs. Lesions were made in the region of the thoracic and cervical cord. He found the sense of touch (Berührungs gefühl) and the response of pain retained. The sense of position (Lagegefühl) was not lost in pure cases. In cases, however, where the lateral columns were also involved there was also a loss of sense of position. Equilibrium usually showed no abnormality. Pure cases usually showed no other type of abnormality, except for a slight temporary disturbance of gait in the animal. No marked disturbances were seen in gait or in the finer isolated movements. These results, according to Borchert, were to be contrasted with the findings of Schiff and were more in agreement with the physiology of man. In man, according to Borchert, there may be retention of touch even with degeneration of the dorsal columns. Touch must therefore be considered as being carried along other pathways, probably of the second or higher order, but not along the long ascending first order fibres of the dorsal columns. It is possible, according to Borchert, that there is some diminution in the sense of touch, but it is rather qualitative than quantitative. We may note that only two of Borchert's animals, in one of which the lesion was performed in the cervical region, appeared from the author's report to be pure cases. The others usually showed some complicating lesions, particularly injury of the lateral columns.

Borowikow [17] found after cutting the dorsal columns that touch (Berührungsgefühl) was retained, but that "muscle sense" disappeared or was considerably diminished. In addition, general equilibrium and co-ordination of the movement appeared to be destroyed.

Bechterew [18, 19] felt that the main criticisms of Schiff's work can be based upon two points.

(1) On the absence of microscopical controls which would probably have revealed in most cases a simultaneous lesion of the lateral columns.

(2) On poor and inadequate methods for testing the various types of loss, especially the type of touch loss supposedly associated with cortical reception. For this Schiff used the reaction to tactile stimuli, which, according to Bechterew, is in all probability a reflex not requiring the cortex for its elaboration.

Bechterew reported observations on section of the dorsal columns in pigeons, rabbits and dogs, in the cervical region. In general, he found evidence of disturbance of equilibrium and co-ordination. In animals in which he checked the lesion microscopically, and in which there was a lesion of the dorsal columns, there was usually a loss of muscle sense and involvement of tactile sensation associated with ataxia. Many of these animals he described as showing the ataxic gait of tabes. In his animal protocols he describes, for example, in a lesion at the level of the fourth thoracic vertebra, a side to side swaying of the body. The movements of the hind limbs appeared somewhat difficult and the swaying increased when the eyes were closed. There were no symptoms of paralysis. Bechterew concluded on the basis of his own and similar experiments performed by Cudnowski in his laboratory, that the dorsal column undoubtedly conducts muscle sense and in part tactile sensibility. With time the disturbance of the sense of position and of movement decreased, and after six weeks the animals appeared entirely normal. The sense of pain was usually completely retained, but thermal sensibility was changed. He reported one case in which unilateral section of the column was made, and in this case disturbance in position and movement occurred only on the side of the lesion, or possibly to a slight degree on the other side. He concluded from this that the major conduction of muscle sense is uncrossed in the dorsal columns. The tendon reflexes were retained in all experiments in all animals operated upon even if the section were performed in the upper lumbar cord. Bechterew concluded, therefore, that the paths associated with tendon reflexes took a short, if any, course in the dorsal columns. Since the work of Bechterew practically no experiments have been reported on the effects of lesions of the dorsal columns.

In man most of the lesions of the dorsal columns have been performed by nature, and in the standard textbooks on neurology, such as that of Tilney and Riley [20], one may find the statement that the function of the dorsal column is the transmission of impulses associated with various discriminative forms of sensation, including that of position

and movement, discriminative touch, &c. It may be of interest here, however, to mention the work of Kroll [21], in which section of the dorsal columns in man was associated with a definite diminution in the number of pressure spots on the skin below the lesion. Foerster and Gagel [22] found evidence that some transmission of pain possibly occurred through the dorsal columns in a small aberrant bundle of fibres which bends out of the antero-lateral column.

Experiments on stimulation of the dorsal columns, in which numerous reflex movements were obtained by workers such as Van Deen, Longet, Brown-Séquard and others, may be dismissed on the ground that improper localization and control of the stimulation both as to intensity and extent make such experiments of little value as evidence of the normal functions of the dorsal columns.

In our survey of the literature we have been unable to find any reference to the effects of lesions of the dorsal columns in monkeys or in the higher apes.

III.—Experimental Material.

Macacus rhesus monkeys, averaging from 8 to 10 lbs., were used in the experiments. They were subjected to no special training before the operations. All operations were performed under ether anæsthesia and with aseptic technique. The operations were done as simply and rapidly as was consistent with obtaining the desired result. The levels at which lesions were made were the fourth or fifth cervical segments and the mid-thoracic region, so as to involve respectively both lower and upper extremities or only the lower extremities, and in the upper lumbar region. After removal of two or three vertebral laminæ at the level chosen for the lesion the dura was split in the midline, the arachnoid carefully removed. The dorsal columns usually could be well seen between the dorsomedial lines of attachment of the entering dorsal roots. Before making the lesion the dorsal vessel of the cord was usually freed with its arachnoid from the cord and retracted, thus being spared in the lesion. When the purpose of the lesion was completely to destroy the dorsal columns, the actual cut was made with an arrow-shaped knife, sufficient in size to sever the columns completely at the level chosen. Occasionally, however, the lesions were made with a small Bard-Parker knife, using a blade No. 11. The columns were usually simply sectioned and none of the dorsal column substance was removed. In most cases a mark was made on the blade to indicate the depth to which the knife would have to go in order to complete the section. Usually very little bleeding occurred following the lesion and

very little swelling of the cord took place immediately after the section. In general the dura was not closed since it was found in a few earlier experiments that the fine black silk sutures used to close the dura occasionally produced additional secondary cord lesions. The muscles were approximated with silk or catgut sutures and the wound closed with Michel skin clips. The wound was simply dressed with iodine followed by powdered boric acid. No bandage of any type was used. With such simple methods, good lesions were generally obtained. No infections occurred in a series of over twenty monkeys, and in no case was the wound opened either by trauma or by the monkey itself.

The animals were observed while coming out of the anæsthesia. They usually had recovered completely by one hour after the end of the operation. The first complete examinations of the animals were made at the three-hour stage when the effects of the anæsthesia had apparently completely disappeared. Subsequent observations were made daily up to the time of sacrifice of the animals. In monkeys which were studied by the Marchi method, the animals were sacrificed from about the twelfth to the sixteenth day. Immediately after death from ether the animals were perfused with 50 per cent. formalin through the aorta, and brain and cord embedded and stained according to the technique advised by A. T. Rasmussen [23]. In general excellent results were obtained with the Marchi stain. Serial sections of the lesion and of sections of the cord at various levels above and below the lesion were made. In particular, the termination of the degenerated portions of the dorsal columns in the medulla were studied serially. Other animals were studied by the Weigert method; some were allowed to live for various periods, some well over six months, in order to observe the improvement which occurred and to allow subsequent operations on other portions of the sensory system, and in them the usual Weigert technique was used.

Moving pictures were taken to illustrate all of the characteristic features of each animal both in the acute and chronic stages. In general, a complete neurological examination was performed on every animal. This consisted of careful observation of the spontaneous behaviour of the animal both as regarded posture and locomotion on the ground and in climbing about the cage. Usage of the limbs, muscle tone, deep reflexes including the arm and knee jerks, the condition of the grip, the ability to climb along a bar, the ability to jump and swim, the special reflexes including hopping, placing, falling and righting reflexes and the various labyrinthine position reflexes studied by Magnus in his vestibular animals were all carefully investigated on each animal.

In order to demonstrate the characteristic symptoms, a typical protocol from each operation will now be presented. These include an animal with a complete section of the dorsal columns at the fourth cervical segment, an animal with section of the columns of Burdach alone at the fourth cervical segment, an animal with complete section of the dorsal columns, and therefore essentially the columns of Goll, at the seventh thoracic segment, and finally an animal with section of the dorsal columns in the upper lumbar region.

Protocol No. 1.—*Monkey Cer.* 80, *January* 12, 1933.

Operation: Complete section of the dorsal columns at the fourth cervical segment. As the animal was coming out of the anæsthesia it showed marked generalized inco-ordination, falling about to one or the other side, and random movements of the limbs with relatively little use of the fore limbs. Each time it made some effort to stand it fell over quickly to one or the other side.

Three hours after operation.—The animal was well out of the anæsthetic. There was seen to be a very marked general disability. It preferred to lie in the cage, making feeble efforts occasionally to stand but not succeeding very well. Its posture was predominantly that of flexion. The fore-limbs were held flexed at the elbow in almost a hemiplegic position with flexion at the wrist. No effort was made to use the limbs spontaneously. The hind limbs were held in a more extended position but very slight co-ordinated movements were made with these limbs. The animal made no successful attempt to climb about the cage at this stage. It appeared not to know what to do with the limbs. An attempt to induce it to grasp the wire sides of the cage was unsuccessful. When dropped head first, with eyes open, only very slight movements of extension were made with the limbs. Placing and hopping reflexes were completely absent in both front and hind limbs. The animal could not right itself when placed on its back. An attempt was made to right the monkey by rotation of the head toward one or the other side, but in no case did the limbs follow the head successfully. So far as could be determined roughly, the animal could feel touch and pain. This was tested by holding the animal so as to cut off the visual element and then watching the eyes while one of the observers either pinched the animal or pricked it with a pin. Movements of the eyes in response to this were observed. It thus appeared that the animal could feel pain and also could feel touch. When the limbs were moved slowly, how-

ever, under similar conditions, the animal appeared to be unaware of this and made no attempts to oppose the change in position of the limbs. This was especially true if the changes in position were made slowly so as not to transmit the sense of movement to too large a portion of the body.

Muscle tone showed a definite decrease in all four limbs. This diminution appeared even greater in the front limbs, although the diminution in the hind limbs was very definite and of a marked degree. Deep reflexes on the other hand were very active. The knee-jerk appeared pendular and very active, possibly even more active than the normal knee-jerk in the monkey.

January 13, 1933: *Twenty-four hours after operation.*—The condition of the animal was still essentially the same, except for the fact that it attempted to right itself more often and made rather ineffectual efforts to move about the cage.

January 17, 1933: *Five days after operation.*—During the past four days the animal made more and more attempts to right itself and use the limbs to some extent. To-day, however, was the first day in which the animal sat up successfully. As yet it has shown no ability to use the fore limbs as single flexible prehensile organs, all food being taken directly into the mouth. The difference in the ability to use the front and hind limbs has been shown during the past few days by the animal occasionally moving itself about the cage by a pushing movement with the hind limbs. The front limbs always remained adducted and in the semiflexed and motionless posture. The hands were open and no flexion of fingers was noticed. These were not used at all for any type of movement of support and it appears that the animal was not aware that it had front legs. In sitting the hind legs were widely abducted without the flexion attitude which was so marked in the front limbs. The animal when placed upon the floor made feeble efforts to move about. When it attempted to stand up it did so only on the two hind limbs with a very broad base. The only movements made by the animal consisted of slight attempts at hopping along the ground and also occasional jumping, which was done entirely with the hind legs. When the animal jumped, however, it fell over to one or the other side and never made well co-ordinated jumps using all limbs. When the animal was held up against the cage to test its ability in climbing, it could not grasp the wire cage with its fore-limbs. The same thing occurred when the animal was placed on the horizontal bar and allowed to drop. The only movements observed

then consisted of gross types of supporting movements made almost entirely with the proximal portions of the limbs. No attempts were made to grasp the bar actively with either the front or the hind limbs. All the special reflexes, including hopping, placing and position reflexes, were as reported at the three-hour stage. The righting reflex had apparently returned to some extent as the animal could now turn over on to its stomach, by coarse, poorly co-ordinated movements when placed on its side. The head, however, appeared to be well oriented in space as all position reflexes on the head appeared normal. Muscle tone persisted definitely diminished. Deep reflexes similarly remained active.

The chief elements in the picture at this period, which might be classified as typical of the acute stage, were the absence of spontaneous movements of the prehensile type in all limbs, especially marked in the fore limbs, loss of the sense of position as tested by slow movement of the limbs, the characteristic posture in the front limbs, the absence of spontaneous grip in all limbs, the generalized hypotonia, the retention of response to pain and deep touch with the absence of the placing and hopping reflexes, and finally the retention of good active knee-jerks.

January 26, 1933: *Two weeks' stage.*—The animal had made slow improvement since the fifth day. The most marked improvement was in its attempts to walk, which it does fairly well at the present time. The animal walked about entirely with the hind limbs, the gait being essentially hopping, resembling the gait of a kangaroo, the front limbs being held in a fairly flexed posture, hypotonic and useless, at the sides. When the animal made any efforts to use the front limbs in walking it usually fell over, since no well coördinated movements could be made with these limbs. However, it jumped about remarkably well, the hind limbs showing considerable spring, with, however, rather poor coördination on the part of the rest of the body. For example, if the animal attempted to jump into its cage from the floor it usually jumped too far or too much to one side, thus missing its goal.

When the animal was placed on the horizontal bar to-day, it was able to hang there by supporting itself entirely with the proximal portions of the limbs, that is the upper arms and the thighs. When attempts were made by the monkey to grasp the bar, the grasping was done almost entirely with the proximal portions of the limbs, and even if some other object such as a bar were brought toward the animal, the animal made groping movements with the limbs without actually grasping the bar actively. If, however, the feet or hands of the animal were

placed around the bar and the animal was then allowed suddenly to drop, it failed to support its weight. As yet the animal has made no attempt to feed itself with the hands, always reaching over with its head to pick up food. Sensory responses have been consistent in showing a retention of pain and touch and a definite loss or marked diminution in the sense of position. The main improvement during the past ten days has been the development of a hopping gait, mainly with the use of the hind limbs. Otherwise the main deficiencies in this animal, the inability to grip, lack of spontaneous prehensile type of movements, the loss of sense of position, the hypotonia, and the sensory loss, have remained the same.

February 12, 1933: *One month after operation.*—The animal has now developed a satisfactory gait, but with a tendency to retention of hopping, using mainly the hind limbs. During the past week it has to some extent used the front limbs in walking. These were rather clumsily used with a tendency towards slipping out to one or the other side. The front and the hind limbs showed a tendency to place in walking the dorsum of the foot against the floor. This has not been so noticeable in the hind limbs as in the front limbs. The characteristic loss of spontaneous grasping movements, especially with the front limbs, have still persisted. The hands, however, have been used to a slight extent during the past three or four days, in bringing food to the mouth, and in sliding the food along the floor of the cage. As yet the animal has shown no ability to reach out and grasp food with the fingers as a normal animal would do. The arm has been used as an implement to direct or support the food on its way to the mouth. Fine movements of the fingers have been absent.

When examined to-day the animal showed some ability to climb along the bar, never, however, upon the bar, but always hanging below it. The proximal segment type of support as previously described still remained. If the animal were teased with a stick, vague defensive movements were made in which the animal warded off the stick with the fore arm or with the upper arm without actually grasping the stick with the hand as a normal monkey would do.

The animal retained, however, some power to hang suspended from a bar, especially if the hands were placed around the bar first and then the animal was allowed to drop suddenly. Responses to pain and deep touch were still as described at the earlier stage and the animal still failed to notice slight slow changes in the positions of the limbs. Muscle tone was definitely diminished in all limbs and the deep reflexes still

were good. If the animal were placed up against the wall of the cage it showed some ability to grasp the wall of the cage with all four limbs, although the grasp with the front limbs was definitely deficient. Once the animal had succeeded in grasping hold of the cage, it apparently could go no further. Coördinated movements of climbing were absent.

When the animal was placed in a tank of water for a swim it showed rhythmic movements in all limbs and it did not appear in danger of drowning like a monkey with loss of vestibular function. This was probably due to the fact that the animal could keep its head oriented in the water, whereas the vestibular monkey could not.

April 12, 1933: *Three months after operation.*—The animal during the past two months has continued to improve slowly, especially with regard to the use of its limbs. The front limbs still have shown much more defect than the hind limbs. Incomplete coarse grasping movements have become possible. The animal has improved in its ability to use the limbs in bringing the food to its mouth. During the past month it has learned to sit up in the corner of the cage with the front limbs resting on the sides of the cage. During the past two months the animal has learned to jump about remarkably well, and the front limbs have also been used more in locomotion. The main deficiencies when the animal walked have been the lack of spring in the front legs and the constant slipping out of the limbs with the tendency to walk on the dorsum of the foot. It has shown some power to climb along under the bar, although the firm, precise, co-ordinated grasping of the bar with the digits of the front or hind feet has been impossible. It has only been during the past two weeks that the animal has shown definite improvement with regard to the use of the hands. At the present we may say that the predominant elements in the picture are the relative inability of the animal to climb about while hanging on the sides of the cage; a definite loss of the sense of position in the limbs as manifested by the occasional passive acceptance of abnormal postures such as walking on the dorsum of the foot, and the persisting hypotonia with active reflexes. The chief defect in the limbs is probably a loss of sense of position and movement.

July 12, 1933: *Six months after operation.*—The animal reached its stage of maximum improvement between the third and fourth month when it attained some ability to climb about on the cage. Walking, however, still retained the hopping character. More definite grasping movements had become possible with the front and hind limbs. The animal reached for food and brought it to the mouth, although these

movements were rather coarsely executed. The hypotonia still persisted. The deep reflexes appeared exaggerated, but the hopping and placing reflexes returned to some extent at about the third or fourth month, especially when the animal was tested with the eyes open. It is of interest that when the animal was allowed to walk about or jump about with the eyes blindfolded there was a considerable increase in its deficiencies. The front limbs tended to return to their original flexion posture.

The main points which characterized the animal at this stage

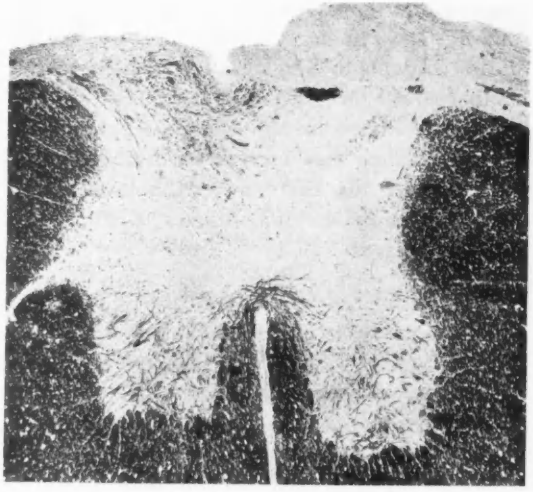

FIG. 1.—Section of the cervical cord at approximately one-half segment above the level of section of the dorsal columns showing the complete degeneration of the dorsal columns. Weigert preparation.

were deficiency in spontaneous fine grasping movements and in fine co-ordinated movements of the limbs as in climbing along under a bar, a clumsiness and stumbling in fast movements, a lack of spring in the limbs, especially in the front limbs, in jumping, with a tendency toward spreading of the limbs, a persistent hypotonia with active deep reflexes and, finally, a retention of pain and touch sensibilities. All of the deficiencies increased when the animal was blindfolded.

Two weeks later the animal was killed and perfused with formalin to be studied in serial sections with Weigert's stain.

Anatomical Study.

Macroscopically, the lesion is confined to the fourth cervical segment. There is a slight amount of scar tissue on the dorsal aspect of the cord. The remaining portion of the cord above and the whole cord below the lesion appear of normal size with no other evident abnormality. Histologically the lesion is found to have completely severed the dorsal columns at the level of the fourth cervical segment. Below the lesion there is no evidence of involvement of the pyramidal tract. Above the lesion the degeneration of the dorsal columns is seen to be complete and there is no evidence of involvement of the dorsal-spino-cerebellar tracts. The degeneration of the dorsal columns immediately above the lesion can be seen from fig. 1. The degeneration can be easily followed to the termination of the columns in the nuclei of Goll and Burdach in the medulla. The anatomical picture just described is typical of complete lesions of the dorsal columns in the cervical region. In other cases where the Marchi method has been used, similar pictures showing complete degeneration of the columns at the level of the lesion and subsequent degeneration to the termination in the medulla could be easily followed.

Protocol No. 2, Cer. 82: February 13, 1933.

Operation: A lesion was made at the fourth cervical segment so as to divide both columns of Burdach. The most medial point of the lesions coincided on the dorsal aspect of the cord with the dorso-lateral sulci.

Immediately after operation the animal showed a severe hypotonus of the front limbs and weakness of these limbs with relatively little motion. When the animal was coming out of the anæsthesia the hind limbs were moved vigorously and frequently. No general postural defects could be seen.

Three hours after operation.—The animal was well out of anæsthesia, and was sitting up in the cage. There was relatively little involvement of the hind limbs. The abnormality seemed to be confined to the front limbs. The animal when sitting up held the front limbs in a flexed position resembling that of Cer. 80 in Protocol No. 1, described above. The hind limbs apparently retained essentially normal posture and the animal used them quite freely. In gait the animal showed a great difference as compared to Cer. 80. In the first place, the hind legs seemed to be relatively slightly involved, apart from a slight general instability and tendency to stumble when the animal was moving fast.

The animal walked about and even the involvement of the front limbs appeared to be slightly less than might have been expected from complete lesions of the columns of Burdach, assuming that the columns of Burdach contain the whole afferent proprioceptive nerve supply from the upper limbs. The front limbs were used to a slight extent in walking. When the animal attempted to walk on all fours, the movement in the hind legs appeared entirely normal, but those of the front legs appeared very deficient. There was slipping out of the front limbs, marked uncertainty in every position, and a tendency for the animal to walk on the dorsa of the feet. The grip in the front limbs was absent, that in the hind limbs was relatively well preserved. When jumping for the cage or attempting to jump up the side of the cage, the animal showed a complete lack of ability to climb with progressive movements of the front limbs. It could not hold on to the cage. The hind limbs obtained a good grip on the wall of the cage, and if the animal were allowed to drop it hung successfully by the hind legs with head down. The animal could hang from the bar by the hind limbs but not by the front limbs. The muscle tone in the front legs appeared definitely diminished. The deep reflexes were active. The muscle tone in the hind limbs was normal. The animal responded to pain or touch on practically every portion of the body, including the upper extremities and trunk. With vision excluded, the animal made no attempt to correct positions impressed upon the front limbs, but did so immediately in the case of hind limbs. The hopping and placing reflexes were absent in the front legs and present in the hind legs. No abnormal vestibular reflexes were present.

February 14, 1933: *Twenty-four hours after operation.*—The general condition of the animal was still essentially the same except that it has been moving about the cage and that it has been using the upper extremities slightly to bring food toward the mouth. The movements were essentially those of support for the food rather than active grasping. The general involvement of the animal does not seem to be as severe as in the animal in which the entire dorsal columns were severed at the same level. This is due to the fact that the operation was confined almost entirely to section of fibres from the upper limbs. Therefore, the trunk and the hind limbs are relatively normal. The occasional stumbling and clumsiness and ataxia in the hind limbs is not very marked.

February 21, 1933: *One week after operation.*—The animal has improved considerably, especially in walking and jumping. It could jump

accurately into the cage and could use the hind limbs for movements of prehension. In taking food the fore limbs were used to support it rather than to grasp it accurately. The grip of the front limbs was poor except when the object to be grasped was firmly placed in the hand and the animal was allowed to drop or was suddenly startled. The animal has not as yet shown any ability to climb up the side of the cage except with the hind limbs. The front limbs were still relatively useless for active climbing. The muscle tone was decreased. The sense of position was definitely diminished in the front limbs, whereas touch and pain were

FIG. 2.—Section of the cervical cord at approximately the level of the lesion showing involvement of both columns of Burdach in a practically symmetrical lesion. The columns of Goll are free, as is the grey matter. Marchi preparation.

retained over the trunk and fore and hind limbs. The symptoms were essentially symmetrical in the fore limbs.

February 27, 1933: *Two weeks after operation.*—The essential findings have remained the same with some improvements in the use of the front limbs. As yet they have not been used successfully for active fine grasping movements or in climbing up the side of the wire cage. Spontaneous grasping has not returned to any great extent. The hind limbs appear now to be relatively free from any abnormality. The defects seem to be confined to the upper extremities where the involvement is relatively severe, consisting of the defects noted above with retention of deep reflexes and deep touch and pain sensations. The

special reflexes, including the extension of the limbs on righting of the animal, are not very active. On dropping the animal, head first, with eyes covered, there is slight extension of the front limbs.

Anatomical Study.

The animal was killed with ether and perfused with 50 per cent. formalin. The spinal cord shows a macroscopic lesion at the level of the fourth cervical segment, in the area of the dorsal columns. Histologically, the lesions are seen to involve both columns of Burdach at the same level. Fig. 2 shows the level of the lesion and fig. 3 the

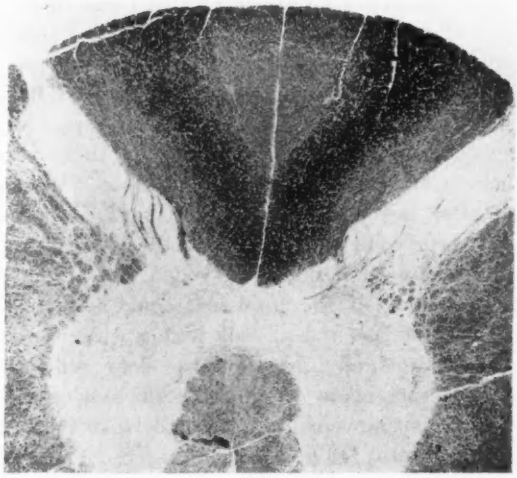

FIG. 3.—Section of the cervical cord at approximately two segments higher than the level of fig. 2, showing the ascending degeneration in the columns of Burdach. The degeneration is seen to be symmetrical. The normal fibres which entered above the lesion are seen ventrolateral to the degenerating ascending fibres. The columns of Goll are free. Marchi preparation.

degeneration involving both columns of Burdach about a segment above it. This degeneration can be traced to the termination of the columns of Burdach in the nuclei of Burdach proper and the nuclei of Clarke-Monakow. Sections taken below the lesion show no evidence of degeneration of the pyramidal tract.

Protocol No. 3, Cer. 135. August 11, 1933.

Operation: Section of the dorsal columns at approximately the seventh thoracic segment. After the lesion there was slight swelling of the cord, with some bleeding.

Immediately after the operation, when the animal was coming out of the anæsthesia, there appeared to be a marked degree of weakness and disuse in the hind limbs which appeared flaccid and were not moved to any extent as compared to the relatively normal movements of the front limbs. No asymmetry in posture was present.

Three hours after operation.—With the animal well out of anæsthesia, the symptoms were confined to the hind limbs, the front limbs being normal except for a certain degree of instability or clumsiness on walking, which seemed dependent upon the relative uselessness of the hind limbs. The hind limbs showed a marked absence of spontaneous purposeful movements, and they often assumed slightly flexed postures both at the thigh and knee. With vision excluded, relatively abnormal postures of the limbs could be superimposed without the animal attempting to correct them. Changes of position likewise could be imposed without any apparent notice on the part of the animal. The animal, with vision excluded, responded with movement to deep pin prick, pinching, and pressure on the hind limbs. When it attempted to right itself after being placed upon the back, incoördinated movements of a coarse type were performed with the hind limbs. Movements of the front limbs appeared normal. When the animal was made to walk a marked weakness of the hind legs could be seen. There was a tendency to drag these legs and to walk with a wide base. Muscle tone was diminished in the hind limbs, but the deep reflexes were active. When the animal was made to climb on the side of the cage normal grasping and climbing movements were made with the front limbs, but the hind limbs were dragged and used clumsily. There was very little spontaneous grasping with the hind limbs. Hopping and placing reflexes were absent in the hind limbs and present in front limbs. In falling with the eyes closed extension of the hind limbs occurred but was slight in degree.

August 12, 1933: *Twenty-four-hour stage.*—Essentially the same findings were present to-day with the difference that the animal stood up on the hind limbs and apparently had comparatively more use of these limbs than had the previous animal of its front limbs following section of the columns of Burdach. The animal still showed loss or marked diminution of the sense of position and of ability to grasp things accurately and spontaneously. Sensory examination revealed the same type of involvement as before. The animal used the hind limbs progressively in walking on all fours, but stood and walked with the toes of the hind feet bent under. The front limbs were free from abnor-

mality. The diminution in muscle tone and the active knee-jerks persisted in the hind limbs. It climbed along quite readily under a bar with the front limbs and showed some ability to hang with the hind legs, but the hanging was done with the proximal parts of the limb rather than with the feet. The tail showed a diminution in balancing movements and in the wrapping of the tail around the wrist on contact.

August 18, 1933: *One week after operation.*—The animal has improved rapidly. It now walks with ataxia, and shows a deficiency in spontaneous grasping movements. The sensory and other reflexes have

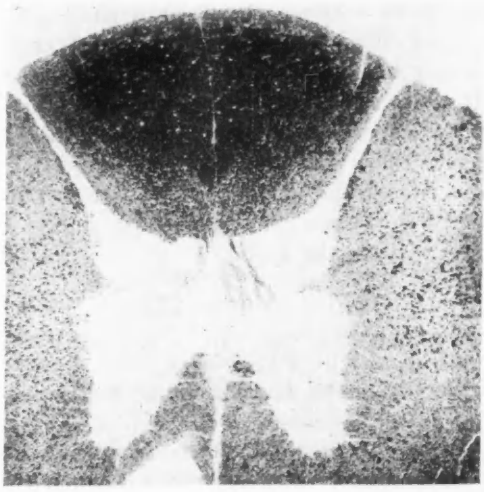

FIG. 4.—Section of the thoracic cord one segment above the level of the lesion in the dorsal columns at the 7th thoracic segment, showing complete degeneration in the dorsal columns at this level. Marchi preparation.

remained unchanged. Muscle tone is diminished in the hind limbs. The knee-jerks are active.

August 25, 1933: *Two weeks after operation.*—It is difficult at this stage to compare the intensity of involvement of the hind limbs with that of the front limbs following the lesion of the column of Burdach. The involvement is not as marked, and the limbs seemed to be used moderately well but with some incoördination. There is diminution of the sense of position, hypotonia, and a tendency towards abduction on walking. The limbs are not used successfully as prehensile organs. Such acts as climbing are done with the proximal parts of the limbs.

The postural defect which was obvious in the upper limbs when the cervical segments were injured was not present at this stage in the lower limbs. The animal was able to employ its hind limbs in standing and walking, and the hopping and placing reflexes, which were absent for a long period after section of the fibres of the dorsal columns from the upper extremities, returned earlier in this animal.

Anatomical Study.

The animal was killed for study with serial Marchi sections. The lesion was found to be between the seventh and eighth thoracic segments, involving the dorsal aspect of the cord and extending slightly into the grey matter to involve some of the cells of Clarke's column. This produced some ascending degeneration in the dorsal spinocerebellar tracts, which are not directly involved by the lesion. There is no degeneration below the lesion in the pyramidal tracts. The degeneration can be followed upward to the termination of the nuclei in the medulla. Fig. 4 shows the degeneration in the dorsal columns about one segment above the lesion.

Protocol No. 4, *Cer.* 110. *June* 17, 1933.

Operation: Section of the dorsal columns between the L 1 and L 2 segments.

Three hours after operation.—The behaviour of this animal resembles so closely that of the animal in the previous protocol that it would be impossible to tell them apart. The same diminution in spontaneous movements, loss of sense of position, hypotonia, and active deep reflexes were present in the same degree.

June 29, 1933: *Twelve days after operation.*—The animal's behaviour has taken the same course as that of the previous animal. The symptoms are confined to the hind limbs and consist of inability to use the limbs accurately for grasping, hypotonia, assumption of abnormalities of posture, with retention of deep reflexes and of pain and tactile sensibilities.

This animal showed the same degree of disability in the hind limbs as did the animal with the lesion in the lower third of the thoracic region. The integrity of four or five thoracic segments had no influence on the symptoms.

Anatomical Study.

The cord was studied with the Marchi method. The lesion was seen to section the dorsal columns and to be confined to these. The degeneration could be easily followed to the nucleus of Goll in the medulla.

These four protocols demonstrate the essential features of lesions in the dorsal columns. Other lesions, or combinations of such lesions, were produced, including section of the column of Goll in the cervical region, section of part of the dorsal column in the thoracic region, hemisection of the dorsal columns, &c., but the essential features of the lesions and of their effects have been illustrated sufficiently by the four protocols presented.

IV.—Discussion.

In general we may say that the uniformly characteristic symptoms presented by our animals with lesions of the dorsal columns were: (1) loss or diminution of the sense of position or of movement, or of both, in the limbs involved; (2) loss or diminution of active spontaneous grasping in these limbs; (3) hypotonia; (4) retention or even increase of the deep reflexes; and (5) loss or diminution of the placing and hopping reflexes in the limbs involved. This complex symptomatology appears to be mainly dependent upon involvement of the sense of position or perhaps of movement, or at any rate of a sense which enables the animal to appreciate postures of the limbs and continuity of movement. Especially in cases where the impulses from the upper extremity are involved, the animal does not appear to be able to accomplish successfully, or even to initiate, the finer types of spontaneous movement, such as grasping. On the other hand, there is no definite paralysis. Further evidence in favour of the origin of the symptoms from lesions of the dorsal columns comes from other animals in which we have recorded similar findings following lesions of the postcentral convolutions, or of the dorsal column nuclei in the medulla.

We have not described the animals as having ataxia after the operations, because we feel that from the physiological standpoint it is better merely to describe what an animal can or cannot do rather than to label it with a word which merely means "a lack of order," and connotes some hypothesis as to its origin. Clinically we speak of "spinal" or "cerebellar" ataxia, according to whether the disorder is associated with a lesion to the dorsal columns or with a lesion of the cerebellar system. This

differentiation is not entirely justified in our observations. We conclude from our anatomical work that the dorsal columns in the cervical region carry an important cerebellar component as well as the deep conscious components of sensibility from the upper extremities. Thus a lesion in the dorsal columns in this region produces an ataxia due in part to involvement of cerebellar components as well as of strictly dorsal column or sensory components. The sharp differentiation into two types of ataxia would not, therefore, be justified in these cases. On the other hand, when the lesion of the dorsal columns is confined to the lower cord, where the dorsal columns component to the cerebellum is not present, the incoördination may more properly be spoken of as a " spinal ataxia " in the usual sense of the term, the cerebellar ataxia developing only if there be an additional involvement of the cerebellar pathways in the lateral columns.

Space does not permit here of a discussion as to the relationship of sensory defects of various types to abnormal movements. As stated above the fundamental defects in the motor behaviour of our monkeys, particularly in those with lesions in the dorso-lumbar region, seemed to be due to some defect of deep sensibility.

The more superficial forms of sensation, such as pain and diffuse touch, seemed to be intact after the operations. However, our methods of testing for these were very gross and it is possible that quantitative defects occurred in these forms of sensation not revealed by our experimental techique. It has been mentioned that pinching of the dorsal columns is associated with a painful sensation. Many of our monkeys jumped violently at the moment when the lesion was produced in the dorsal columns even though they were under deep anæsthesia. As stated before, Kroll found a definite diminution in the skin pain spots below the level of the lesion when he sectioned the dorsal columns in the human subject. It is possible, therefore, that owing to a diffuse distribution of pain tracts only a slight loss of pain sensibility would result from lesions of the dorsal columns, and that a large lesion of the spinothalamic tract would be necessary to produce any gross defect of pain such as might be detected in the monkey.

One of the most interesting clinical features in the monkeys was the inequality already mentioned in the intensities of the symptoms in the front and hind limbs resulting from cervical lesions. When the cervical dorsal columns were completely sectioned at a level above that of the zones of entrance of all sensory roots from the fore limbs, for example, at the third or fourth cervical segment, the involvement of the fore

limbs was immeasurably greater than that of the hind limbs, the fore limbs being practically useless at a time when the animal had already learned to jump fairly well on its hind limbs. Then again, when lesions were made in the columns of Burdach alone at similar levels, the involvement of the fore limbs was always much more severe than was the involvement of the hind limbs in cases where the columns of Goll were sectioned above the levels of entry of the sensory roots from the lower limbs.

Bechterew noted severer disturbances in the fore limbs in the dog following cervical dorsal column lesions and attributed this to the short course in the cord of fibres of the dorsal column associated with deep sensations, many fibres from the hind limbs leaving them before reaching cervical levels. With this exception we have been unable to find in the literature any mention of this inequality in intensity of the symptoms between front and hind limbs, and therefore no attempt has been made to formulate any concept as to the functional differences between the posterior columns at high cervical or low thoracic levels. We believe that we can offer an explanation for the differences observed. From anatomical and experimental work which we are reporting elsewhere [24, 25], we have been able to confirm the existence of three main cellular groups in the terminal dorsal column nuclei in the medulla. The first two groups are the well-recognized nuclei of Goll and Burdach proper, which receive the fibres from the columns of Goll and Burdach and send their axons in the main into the medial lemniscus. The third large group of cells has been variously described as the nucleus of Monakow, the nucleus corporis restiforme, the nucleus of Blumenau, the external cuneate nucleus, &c. We prefer to call it the nucleus of Clarke-Monakow, in favour of Clarke who first described it, and Monakow who first established its cerebellar connections. We have been able with four series of experiments to confirm Monakow's view as to its cerebellar connections. We have been unable to determine its afferent spinal connections in the monkey. We have also been able to delimit anatomically the three main groups of cells, and finally we have established the very important direct connections of the nucleus of Clarke-Monakow with the dorsal roots of the cervical and upper dorsal segments of the spinal cord. These connections are established directly through the column of Burdach which sends a large portion of its fibres to the nucleus of Clarke-Monakow in addition to those which terminate in the nucleus of Burdach.

We have thus established that the columns of Burdach carry in addition to the long sensory afferent fibres a large cerebellar component

of afferent fibres from the upper extremities. On the other hand, this cerebellar component from the hind limbs is carried outside of the dorsal columns. A lesion of the dorsal columns in the cervical region will thus interrupt two large and important groups of fibres from the upper limbs, namely, that passing to the nuclei of Goll and Burdach and connected with the medial lemniscus, and that going to the nucleus of Clarke-Monakow and then to the cerebellum. The addition of the cerebellar component in the lesion at this level is not met with in dorsal column lesions in the low dorsal, lumbar or sacral regions, where the cerebellar component travels in the main in the spino-cerebellar tracts. Therefore it may be easily seen that due to the loss of two main afferent components from the upper limbs cervical lesions would be associated with a greater involvement of such upper limbs as compared with the lower limbs.

It is of interest to note here that Bechterew described loss of equilibrium as one of his most constant findings in dorsal column lesions. He attributed this to section of fibres which he believed to pass through the dorsal columns and their nuclei directly into the cerebellum. Although Bechterew was right in attributing some cerebellar component to the cervical dorsal column, the direct cerebellar pathway from the posterior column to the cerebellum, which he used as the anatomical substratum for his explanation, still remains a doubtful one. Many writers have denied its existence. Even the various other connections between the nuclei of Goll and Burdach and the cerebellum such as the internal, external and posterior arcuate fibres, still retain a contraversial status. This is due probably to the absence of absolutely reliable serial sections of brains with localized lesions in the terminal nuclei of Goll and Burdach.

SUMMARY.

(1) As a result of experimental lesions of the posterior columns in *Macacus rhesus* monkeys characteristic symptoms follow, represented mainly by loss or diminution of sense of position and loss or diminution in the ability for spontaneous fine grasping in the limbs involved. There is in addition hypotonus associated with retention, and at times increase, of the deep reflexes and loss or diminution of the placing and hopping reflexes.

(2) The symptomatology following lesions of the posterior columns in the cervical cord above the zone of entrance of the posterior roots for the fore limbs is much more severe in the fore limbs than is the disturbance in the hind limbs following lesions of the posterior

columns in the dorsal or lumbar region above the zone of entrance of the posterior roots for the hind extremities.

(3) The difference in symptomatology is explained by the fact that in the posterior column of the sacral, lumbar and dorsal segments there are only afferent sensory fibres. In the posterior column of the cervical segment, there are also afferent fibres to the cerebellum.

(4) It follows that while the symptomatology resulting from section of the dorsal columns in the dorso-lumbar and sacral region is the expression of what might be termed spinal ataxia, the symptoms following lesions of the posterior column in the cervical region is the expression of both spinal and cerebellar ataxia.

(5) The anatomical pathway carrying proprioceptive impulses to the cerebellum in the posterior column is represented by numbers of fibres which end in the so-called nucleus of Clarke-Monakow from the column of Burdach. The axons of this latter nucleus then enter the cerebellum via the corpus restiforme.

(6) In the cervical segments the posterior columns contain, in addition to the long system of fibres, an important cerebellar component represented by fibres running to the terminal nucleus of Clarke-Monakow. The fibres originating from this nucleus may be considered analogous to the fibres originating from Clarke's columns in the dorso-lumbar segments.

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INORGANIC CONSTITUENTS OF CEREBROSPINAL FLUID *v.* VENTRICULAR AND LOCULATED FLUID.

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THE cerebrospinal fluid is still regarded by many as being formed by ultrafiltration through a non-specific membrane at the choroid plexus. It has been shown, however, in the previous papers of this series (McCance and Watchorn, 1931 and 1932, Watchorn and McCance, 1932 and 1933) that the amount of potassium and of magnesium found in human lumbar puncture fluids cannot be accounted for by ultrafiltration from serum. This was also found to be true of calcium when the serum calcium was very low, and Herbert (1933) has more recently shown that, when the serum calcium is abnormally high or low, ultrafiltration will not explain the amount of calcium found in lumbar puncture fluid. These results may be criticized on the grounds that the fluids analysed had been so changed in their passage from the ventricle to the lumbar region that they no longer represented the true serum ultrafiltrate which had first been formed. It was felt therefore that this possible criticism should be met by a study of these ions in fluids taken from various levels of the cerebrospinal system.

SOURCES OF MATERIAL AND METHODS.

The ventricular and other fluids were almost all from cases of cerebral or spinal tumours which were being operated upon or investigated in some way. The fluids in Table II were all taken under gas and oxygen anæsthesia. The ventricular and lumbar puncture fluids of each case in Table II and the cisternal and lumbar puncture fluids in Table III were taken within a few minutes of each other. Some of the material was obtained from the National Hospital for Nervous Diseases, Queen Square, but the greater part from King's College Hospital. The general technique including the analytical methods has been described in previous papers of this series.

Results.

Table I shows the amounts of potassium, calcium and magnesium which have been found in ventricular fluids. Average values of serum, serum-ultrafiltrates and lumbar puncture fluid from previous papers of the writers have been added for comparison. It will be noticed that the concentrations of the individual ions in the ventricular fluids are close to those of the lumbar fluids and if anything are less like serum ultrafiltrates than are the lumbar fluids. If this is true, then there is a tendency for the fluid to come into equilibrium with the serum during the passage down the canal.

Table I.—Ventricular Fluids.

(All figures represent milligrams per 100 c.c. fluid.)

	Potassium	Calcium	Magnesium
	11·00		
	9·16	7·16	3·44
	10·70	5·78	3·87
	8·80	5·00	3·60
	10·10	4·90	3·44
	12·90		3·26
		5·98	4·19
	12·81		3·44
			3·83
	11·14	5·39	3·79
		6·70	3·53
			3·81
		6·43	4·22
		5·61	4·34
	9·36	5·11	3·59
	10·42		
	10·13		
	10·34		
	11·45	5·29	3·61
	9·15	5·59	3·29
	11·57	5·49	3·01
Average	10·60	5·95	3·66
Average serum value ..	19·70	10·33	2·71
Average ultrafiltrate value	21·20	5·54	2·01
Average spinal fluid value	12·05	5·33	3·22

Table II shows a further series in which comparisons of the ventricular and lumbar fluids have been made on the same case. The results for magnesium and potassium corroborate in every respect those shown in Table I. The average amount of calcium found in the ventricular fluids is slightly below that in the lumbar fluid, whereas in Table I the reverse was the case. The differences are probably not significant.

TABLE II.—CEREBROSPINAL FLUID AND VENTRICULAR FLUID.

	Calcium		Magnesium		Potassium	
	Spinal fluid	Vent. fluid	Spinal fluid	Vent. fluid	Spinal fluid	Vent. fluid
			3·42	3·74	7·96	8·11
			3·39	3·62	7·38	7·31
	5·49	5·49	3·48	3·40	12·11	12·22
	5·48	4·31	2·49	2·59	12·21	10·00
	5·49	5·39	3·07	3·43	10·47	10·23
	6·08	5·98	3·06	3·25		
	6·37	5·39	2·88	3·05		
			3·08	3·17		
Average ..	5·74	5·31	3·11	3·28	10·03	9·57

Since the fluid withdrawn from below a spinal tumour may differ very greatly in colour, protein content, &c., from normal cerebrospinal fluid, it was felt that an examination of these loculated fluids should be made.

Table III (Cases 1 to 8) shows the results which have been obtained. In Case 9 the lumbar fluid was withdrawn from just above the tumour. It will be noted that the amounts of magnesium and potassium resemble those in normal cerebrospinal fluids and not those in serum ultrafiltrates. When both cisternal and lumbar fluids were obtained

TABLE III.—LOCULATED FLUIDS.

Case No.	Calcium Mg./100 c.c.		Magnesium Mg./100 c.c.		Potassium Mg./100 c.c.	Protein grams/100 c.c.
	Serum	C.S.F.	Serum	C.S.F.	C.S.F.	C.S.F.
1 ..	10·41*x*		2·54*x*			
		6·76*y*		3·85*y*		2·7
	9·12*z*		2·51*z*			
2 ..	10·10	6·93	2·72	3·90		1·8
3 ..				3·38	8·40	
4 ..	11·91	5·98	3·21	3·45		
5 ..		6·90		3·62		
6 ..	10·45	6·90	2·91	3·85		0·5
7 ..	11·42	8·06	2·80	3·38		6·4
8 ..	11·32	7·14	2·46	3·54		1·0
		5·91*a*		3·54*a*		0·02*a*
9 ..	9·90	5·78*b*	2·88	3·42*b*	11·01*b*	1·0*b*
		5·10*a*		3·72*a*	12·66*a*	0·04*a*
Average (omitting 8*a*, 9*a* and *b*)	10·45	7·2	2·75	3·55	8·4	
Average of previous figs. for sera and spinal fluids	10·33	5·33	2·71	3·22	12·05	
Average ultrafiltrate ..		5·54		2·01	21·2	

x, *y* and *z* = Taken on successive days.
a = Cisternal fluid.
b = Fluid withdrawn from immediately above the tumour.

(Cases 8 and 9) the differences in protein content and the agreement in magnesium values are very striking. In most of the cases manometric measurements made at the time the fluid was withdrawn indicated a complete obstruction of the canal at the site of the tumour. This may not strictly have been the case, for fluid may have been able to percolate slowly past the tumour. One would have expected, however, that in loculated fluids, if anywhere in the cerebrospinal system, the concentrations of ions would have approximated to those of ultrafiltrates. That they show no tendency to do so suggests that the membranes lining the whole of the cerebrospinal spaces are of a specific character and similar to those of the choroid plexus.

Discussion.

These results enable one to say with confidence that the magnesium and potassium in ventricular fluids cannot be accounted for by ultrafiltration from serum. Since the serum calcium throughout the present series was never grossly abnormal, and since the amount of calcium in the lumbar or ventricular fluid in such cases agrees approximately with that in an ultrafiltrate, it is not possible to be so dogmatic about this particular ion. It is probable, however, that could the ventricular fluids of cases with grossly abnormal serum calcium values be examined, they would be found, like the lumbar fluids, not to follow the serum fluctuations, for there is good reason to suppose that the fluid of the cerebrospinal system has usually the same ionic pattern from whatever source it is withdrawn.

With regard to the loculated fluids, these differ from normal cerebrospinal fluids in two respects: (1) They contain, as is well known, large amounts of protein; (2) they contain, as was pointed out by Critchley and O'Flynn (1924), more calcium (average 7·2 against 5·33 for non-loculated cerebrospinal fluid). One cannot regard these fluids as serum ultrafiltrates since the concentrations of magnesium and potassium are so unlike those of ultrafiltrates. The suggestion has often been made that the protein is derived not from the serum but from the tumour. Our results are in favour of this, since the concentration of magnesium and potassium resemble those of normal cerebrospinal fluid, which one would not expect if such large amounts of protein were leaking through from the blood-vessels. It is possible that the study of other electrolytes now being undertaken may help to supply further evidence. The excess of calcium is probably associated with the increased protein but there is no sound evidence at present as to its source.

SUMMARY.

(1) Ultrafiltration will not explain the amounts of potassium and magnesium found in ventricular fluids. Such fluids in fact appear to contain slightly more magnesium and less potassium than lumbar fluid. As regards these two ions, therefore, ventricular fluid is even less like a serum ultrafiltrate or a pathological transudate than is the spinal fluid.

(2) Judged by their magnesium and potassium contents, loculated fluids taken from below spinal tumours resemble ventricular fluids or spinal fluids and not serum ultrafiltrates. Such loculated fluids appear to contain more calcium than fluids from the ventricles, normal cerebrospinal fluid or serum ultrafiltrates, and this may be connected with their large protein contents.

The authors are greatly indebted to a number of people who have assisted them to obtain the material for this investigation and helped in other ways, especially to Mr. C. P. G. Wakeley, Dr. J. G. Greenfield, and Dr. E. A. Carmichael. One of us (Miss E. Watchorn) has carried out the work during the tenure of a personal grant from the Medical Research Council.

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THE RELATIONSHIP BETWEEN THE SUGAR AND UREA CONTENTS OF THE BLOOD AND CEREBROSPINAL FLUID.

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CONSIDERABLE diversity of opinion prevails as to the relationship between the sugar content of the blood and that of the cerebrospinal fluid. There is also a paucity of records dealing with the comparative urea content of the blood and of the cerebrospinal fluid. In this paper is described a series of investigations undertaken to further our knowledge regarding these relationships in comparatively healthy subjects.

Fremont-Smith and Dailey (1925) were able to demonstrate in three subjects that following a glucose meal the lumbar fluid sugar rose by not more than 6 mgm. while that of the blood rose and fell as in a normal blood-sugar curve. In one subject, the blood sugar was rapidly raised to 290 mgm. per cent. after intravenous glucose; during the ninety minutes following the injection, a rise of 9 mgm. occurred in the fluid sugar. Riser (1929) gives the figures from one case in which he found that the fluid sugar was raised by 3 mgm. following the ingestion of glucose. Findings comparable to the above are also reported by Wittgenstein (1923). In contrast to the above observations, other authors have demonstrated that there is a parallelism between the blood and fluid sugar levels (Schloss and Schroeder (1916), Polonowski and Duhot (1923)). Jacobsen (1932) and Münch-Petersen (1930) record a slight rise after a glucose meal in the lumbar fluid sugar with a greater rise in the cisternal fluid sugar in a series of subjects suffering from epilepsy. With these observations Schjott (1931) agrees, but emphasizes the fact that this disparity occurs more frequently in epileptic than in other subjects. Chevassut (1927) appears to be the only English author to investigate these relationships; she concludes, after examination of single specimens of ventricular fluid and of blood, that the ventricular fluid sugar and that of the blood are identical in the same individual at the same time. The lumbar and ventricular fluid sugars have also been compared by Fremont-Smith and Dailey (1925), Riser

and Merrill (1927), Cestan, Riser and Laborde (1923). Apart from two of the cases reported by Riser and Merrill, the ventricular fluid sugar level has been invariably higher than that of the lumbar fluid. Riser (1929), however, expresses the opinion, as the result of the examination of many fluids, that the sugar in the fluids from these different sites is in equal concentration at any same point of time.

The relationship of fluid urea to blood urea, as determined by an examination of single specimens, has been investigated by Merritt and Fremont-Smith (1934), Cestan, Riser and Laborde (1923), and Levinson (1929), who are of opinion that the lumbar fluid urea content is similar to that of the blood.

Experimental Procedure and Results.

(*a*) *Sugar.*—A series of young adults admitted for non-organic conditions of the nervous system and not suffering from epilepsy were investigated in order to determine the blood and lumbar fluid sugar levels following the ingestion of a known quantity of glucose (50 grm.) after a night's fast. In five, specimens of lumbar fluid were obtained before the giving of glucose and at varying intervals during the period of two hours immediately following. Specimens of blood from the ear were taken simultaneously with the collection of the fluid specimens. During these procedures the subject lay quietly in the horizontal position with the lumbar needle in situ. Similar investigations in four other cases were undertaken; in two, the lumbar fluid was withdrawn at intervals during the period between one and a half to three and a half hours, and in the other two during the period between three and five hours after the glucose meal. From all four subjects, specimens of blood were obtained before the giving of glucose and during the whole three and a half and five hour periods. In another series of seven cases, isolated samples of blood and ventricular fluid were taken simultaneously at varying intervals; in two of these subjects it was possible to obtain samples on different days. All the subjects from whom ventricular fluid was obtained presented symptoms referable to the presence of intracranial tumour.

In one case with considerably increased intracranial pressure, specimens of blood and ventricular fluid were obtained at intervals over a period of two hours. In another case without increased intracranial pressure, it was possible to obtain samples of blood and ventricular

fluid, under fasting conditions and for one and three-quarter hours after a glucose meal.

The chemical estimations for sugar were performed immediately by the method of Hagedorn and Jensen. Two estimations were performed

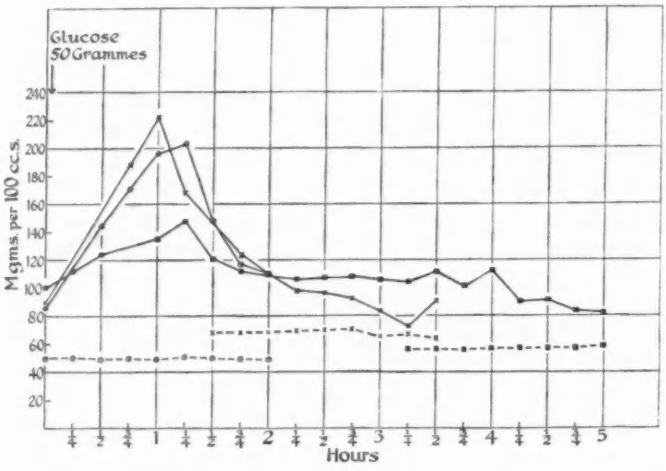

FIG. 1.—The blood sugars are represented by continuous lines and the fluid sugars by interrupted lines.

on each specimen of fluid; the difference between the results of each pair was never greater than could be explained by the limitations of the method. The figures quoted are the mean of the two.

TABLE.

Name	Date	Amount in grm. of glucose given	Time in minutes specimens were taken after glucose meal	Blood sugar in mgm. per cent.	Ventricular fluid sugar in mgm. per cent.
Mr. G.	2.6.34	50	45	156	82·5
	4.6.34	50	25	146	83
	6.6.34	Nil	—	129	90·5
Mrs. M. ..	7.6.34	50	25	167	53·5
	15.6.34	50	10	114	63
Mr. E.	15.6.34	50	35	133	57
Mrs. A... ..	19.6.34	Nil	—	138	82·5
Mr. L.	28.6.34	50	70	120	82·5
Mr. X.	6.7 34	25	80	191	64
Mr. A.	17.8.34	50	65	74	56

An analysis of the results, in the nine investigations dealing with the lumbar fluid, showed no rise in the sugar content of the fluid up to a period of five hours after the glucose meal. Fig. 1 shows typical findings in the blood and fluid from three cases from which specimens were, obtained over a period of five hours.

In the series of cases in which the sugar content in isolated samples of blood and ventricular fluid were estimated, the ventricular fluid sugar has been found to be invariably lower than that of the blood. It was impossible in these cases to obtain a blood sugar curve so that no statement can be made as to whether the blood sugar was rising or falling.

In the subject showing no evidence of increased intracranial pressure and in which a ventricular fluid sugar curve was obtained, the

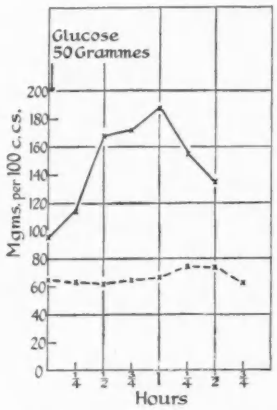

FIG. 2.– The blood sugar is represented by a continuous line and the fluid sugar by an interrupted line.

blood sugar rose and fell as in a normal individual; at the end of seventy-five minutes after the giving of glucose the ventricular fluid sugar content had risen by 9 mgm. when the blood sugar was falling. Thirty minutes later the ventricular fluid sugar had fallen to 2 mgm. below the fasting level (*see* fig. 2). During this investigation there was a continuous small loss from the ventricular needle of 6 c.c. of fluid per hour; this loss may have some bearing on the slight rise in the ventricular fluid sugar level.

The other ventricular fluid sugar curve was from a subject with

increased intracranial pressure. In this case the blood sugar curve was of a mild diabetic type and was still rising at the end of two hours after the ingestion of glucose; the ventricular fluid sugar continuously rose to a lower level.

(*b*) *Urea.*—After a night's fast, a known quantity of urea (30 grm.) was given by mouth to six cases. Specimens of blood and lumbar fluid were taken at identical times before and at frequent intervals following the administration of the urea. In the first two cases, lumbar fluid was obtained immediately before and for two hours following the administration of urea; in the next two cases, the lumbar fluid was withdrawn during the period of two hours commencing one and a half hours after the giving of urea; in the remaining two cases, the lumbar fluid was taken during the period from the third to the fifth hour after the urea meal. In all six cases, frequent estimations of the blood urea were carried out from immediately before the administration of the urea until the withdrawal of the last sample of cerebrospinal fluid.

While it is impossible to keep the blood sugar level constantly rising, it is possible to do this to the blood urea level by the repeated administration of doses of urea by mouth. This method of approach to the problem appeared worthy of trial and six subjects were submitted to the procedure. In two, urea was given twice during a period of three and a half hours and in another thrice within five hours. Each dose of urea was of 30 grm. and was given at about one and a half hourly intervals. In each case, blood urea estimations were frequently made and, once it was found that the blood urea level was high, lumbar puncture was performed and specimens of fluid were taken for the subsequent two hours. In three other cases intensive feeding with urea made it possible to raise the blood urea to an even higher level. In the first of these, 130 grm. of urea in eight doses were given over a period of eight hours, during the last two of which the lumbar needle was in situ. In the second, 155 grm. of urea were given in eight doses during eight hours and specimens of the lumbar fluid were withdrawn during the last one and a half hours; in the last experiment with a duration of ten hours, during the last two of which specimens of lumbar fluid were obtained, 165 grm. of urea were given in ten doses. In all three experiments the blood was sampled frequently and the urea content estimated.

The estimations for urea were performed immediately on the blood and fluid samples by Archer's modification of the method of Folin and Wu. Duplicate specimens of the fluid were estimated in every instance

and the percentage of error was less than that obtained in the sugar estimations.

The six experiments in which a single dose of urea was administered gave results indicating that no rise occurred in the lumbar fluid urea content, either synchronous with or after the rise of blood urea. Fig. 3 gives lumbar fluid and blood urea curves illustrative of these results.

In two subjects, to whom two doses of urea had been given, the blood urea rose from 30 to 124 mgm. per cent., and from 36 to 170 mgm. per cent. respectively. In the former subject, the lumbar fluid urea rose from 28 to 40 mgm. per cent. and was the same in the last two estimations; in the latter subject there was a rise of 4 mgm. in the lumbar fluid over a period of one and three-quarter hours. In the subject given three doses of urea, the fasting blood urea was 50 mgm.

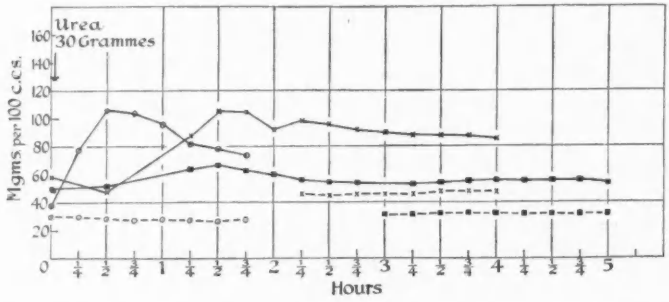

FIG. 3.—The blood ureas are represented by continuous lines and the fluid ureas by interrupted lines.

per cent. and at the end of three and a quarter hours the lumbar fluid urea was found to be 70 mgm. per cent., when the blood urea had risen to 164 mgm. per cent. During the next three-quarters of an hour the blood urea continued to rise to the high level of 234 mgm. per cent. The blood urea slowly fell during the next hour to 194 mgm. per cent., while the lumbar fluid urea rose to 85 mgm. per cent. and remained at that level for the last two estimations.

In the first of the experiments in which intensive feeding over a period of eight hours was practised, the fasting blood urea was 50 mgm. per cent.; this had risen at the end of six hours to 142 mgm. per cent., and thereafter for the next two hours rose steadily, eventually to reach

the level of 178 mgm. per cent. At the end of the sixth hour the lumbar fluid level was 50 mgm. per cent. This corresponded to the fasting blood urea level and as the blood and fluid fasting levels are accepted as being identical it may be assumed that no rise in the lumbar fluid level had occurred by the end of the sixth hour. During the next three-quarters of an hour the fluid urea remained constant, to rise 8 mgm. during the next half-hour and thereafter to remain at this level of 58 mgm. per cent. In the second case, the fasting blood urea was 37 mgm. per cent.; this had risen to 192 mgm. per cent. at the end of six and a quarter hours, after which a fall to 158 mgm. per cent. at the end of the experiment had occurred. The first specimen of lumbar fluid obtained at six and a quarter hours after the commencement of the experiment contained 74 mgm. per cent. of urea; as this is above the fasting blood level it is indicative that a rise in the fluid urea content had taken place at an earlier time. During the next one and a half hours there was a fall of 9 mgm. in the fluid urea content. In the last experiment of intensive and prolonged feeding with urea, the fasting blood urea was 58 mgm. per cent.; at the end of nine and three-quarter hours it had risen to 280 mgm. per cent. Lumbar fluid taken at eight hours contained 80 mgm. per cent., which concentration persisted till the termination of the experiment at ten hours. As the fluid urea was higher than the fasting blood urea, a rise in the fluid level had occurred during the first eight hours whilst the blood urea had been rising. Figures obtained in all experiments not quoted in detail or illustrated in the text will be found at the end of the paper.

Discussion.

It has been shown that the levels of sugar and urea in the lumbar fluid remain constant following the ingestion of known quantities of glucose and urea. The amounts of glucose and urea administered in these investigations produced changes in the blood levels, changes which are comparable to those following the taking of an ordinary meal containing carbohydrate and protein. Consequently it is unlikely that a fluctuation occurs in the lumbar fluid sugar and urea contents in a healthy person during twenty-four hours. The presence, therefore, of a high lumbar fluid sugar or urea becomes of clinical significance. Further the investigations show that marked alterations in the blood urea may occur without any similar alteration in the lumbar fluid. Accordingly in a patient exhibiting an acute rise of the blood urea, a coincidental

and similar rise in the lumbar fluid level is not a necessary concomitant. Neither the sugar nor the urea contents of the lumbar fluid can be taken as indicative of the blood levels.

In the ventricular fluid it is possible to determine a small rise of the sugar content in association with a rise in blood sugar. As the rise recorded in the case without gross disturbance of intracranial pressure was so insignificant, and as during the experimental procedure there was a constant slight leak of ventricular fluid, it is probable, were it possible to examine ventricular fluid without removing any, that the ventricular fluid sugar in health would be found to remain constant in the presence of considerable fluctuation of the blood sugar. But when the blood sugar behaves in an abnormal way or or when evidence of increased intracranial pressure is present, there is not infrequently found a rising sugar content or a relatively high one in the ventricular fluid. No figures are available to permit a statement as to whether the ventricular fluid urea in health rises as the result of a shift normally encountered in the blood urea. From the similarity of the results in the sugar and urea experiments, we are of the opinion that if any rise in the ventricular fluid urea does occur it will be minimal and of no clinical significance.

Do the results of these investigations support any one theory of the origin of the cerebrospinal fluid? When the above results are interpreted in the terms of the dialysate theory of the formation of the cerebrospinal fluid, difficulties are immediately encountered. On the basis of this theory, sugar and urea when increased in the blood should pass through to the cerebrospinal fluid and if the increase in the blood is continuous, a continuous alteration in the fluid should occur until a state of equilibrium is reached. The behaviour of the lumbar fluid sugar and urea as determined in these investigations does not conform to this theory. It is possible that a slow rate of diffusion of these two substances in the cerebrospinal fluid might account for the failure to detect evidence indicating that the lumbar fluid contents approached those of the blood; in other words the time factor may not have been sufficiently investigated. This is improbable as the experiments covered a period of five hours, by which time the blood contents had returned to normal. More important are the observations of the behaviour of the ventricular sugar content after a glucose meal and of the lumbar fluid urea following intensive feeding with urea. In the ventricular fluid it has been demonstrated that, when the pressure is normal, there is no significant rise of the ventricular sugar coincident with that of the blood. It may be suggested that the area of surface,

namely the choroid plexus, through which dialysis can take place, is very small and that the apparently insignificant changes observed in the ventricular fluid are in fact evidence of dialysis; and in support of this could be quoted the observations demonstrating a rise in ventricular-fluid sugar when the blood sugar was abnormal and continued to rise. But the results obtained with intensive urea feeding are of great importance. Urea being more rapidly diffusible than sugar, it is to be expected that the urea content in the lumbar fluid would continue to rise as long as a rise in the blood urea continues to take place. In fact no rise in the lumbar fluid urea occurs in association with the rise in the blood urea when the urea administered is similar in quantity to that obtained from ordinary diets. When intensive feeding of urea is resorted to, the blood urea can be made to rise to a very high level over a period of hours; during the same period the lumbar fluid urea rises only a small amount and may then cease to rise even though the blood urea continues to increase. This finding indicates that the fluid urea does not follow the laws of dialysis. It is apparent, therefore, that the choroid plexus must play an active part in controlling the level of fluid urea and that the choroid plexus does not act simply as a dialysing membrane.

To determine the nature of the functional activity of the choroid plexus by a comparative study of the blood and fluid contents in diabetes and uræmia is open to the criticism that the choroid plexus may be damaged by the disease process. There is histological evidence that in uræmia the cells of the choroid plexus are abnormal. It is impossible to explain by the theory of dialysis the presence in the fluid of a urea content higher than that in the blood. Recently an opportunity was afforded us, in a case of uræmia, to make repeated observations over a period of twenty-four hours on the blood and lumbar fluid urea levels. When first examined the blood urea was 340 mgm. per cent. and the lumbar fluid urea 332 mgm. per cent.; sixteen hours later the blood urea was 523 mgm. per cent., the fluid urea 592 mgm. per cent., and at the last examination, seven hours later, the blood urea was 560 mgm. per cent. and the fluid urea 640 mgm. per cent. In the presence of a continuous rise of blood urea, the fluid urea originally at a lower level eventually rose to 80 mgm. above that of the final blood urea. No evidence was present that any profound change had occurred in the other chemical constituents of the blood; in the absence of such a change, the choroid plexus must have taken an active part in raising the fluid urea above that of the blood. These observations in a case of

uræmia, therefore, uphold our view based on the experiments recorded in this paper that the choroid plexus actively participates in the control of some of the contents of the cerebrospinal fluid and is not merely a passive dialysing membrane.

Summary.

(*a*) A series of investigations are described which have been undertaken to determine the relationship between the sugar and urea contents of the blood and cerebrospinal fluid.

(*b*) It has been shown that the levels of sugar and urea in the lumbar fluid do not rise in association with a normal rise in the contents of these substances in the blood.

(*c*) Estimations of ventricular fluid sugar have been made. These demonstrate that only in abnormal conditions is there any rise in the fluid sugar in association with a rise in the blood sugar.

(*d*) The bearing these findings have upon the theory of the nature of the cerebrospinal fluid is briefly discussed. It is suggested that the findings are in favour of the choroid plexus taking an active part in the control of the level of sugar and urea in the cerebrospinal fluid.

It is with pleasure that we express our gratitude to the members of the staffs of the National and King's College Hospitals for permission to carry out these investigations upon patients under their care.

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SUGAR EXPERIMENTS.

(Time is expressed in hours, and sugar in milligrammes per cent. The glucose meal was given immediately after the first estimation.)

MR. K.

Time	Blood sugar	Lumbar fluid sugar
0·0	74	68
0·5	90	67
0·10	116	62
0·15	122	61
0·20	136	68
0·25	161	68
0·30	177	69
0·35	178	69
0·40	184	70
0·45	200	64
0·50	208	68
0·55	212	70
1·0	206	68
1·5	193	67
1·10	184	69
1·15	176	69
1·20	168	69
1·25	144	71
1·30	130	68

MR. C.

0·0	85	52
0·15	141	51
0·30	177	55
0·45	186	52
1·0	141	57
1·15	110	58
1·30	105	55
1·45	81	58
2·0	79	59

MR. MACR.

0·0	79	—
0·45	163	—
1·0	127	—
1·35	117	50
1·50	111	49
2·5	88	49
2 20	77	48
2·35	79	52
2·50	92	52
3·5	81	54
3·20	79	54
3·35	74	55

MR. B.

Time	Blood sugar	Lumbar fluid sugar
0·0	68	44
0·15	135	48
0·30	174	46
0·45	160	47
1·0	115	48
1·15	100	47
1·30	96	52
1·45	82	51

MR. E.

0·0	95	64
0·15	114	66
0·30	142	67
0·45	178	69
1·0	197	67
1·15	223	65
1·30	200	64
1·45	178	64

MR. H.

0·0	77	—
0·30	104	—
1·0	126	—
1·30	114	—
2·0	86	—
2·30	75	—
3·0	73	50
3·15	86	56
3·30	92	55
3·45	104	57
4·0	95	59
4·15	86	57
4·30	93	55
4·45	104	54
5·0	86	57

CASE WITH INCREASED INTRACRANIAL PRESSURE AND EXHIBITING A BLOOD SUGAR CURVE OF MILD DIABETIC TYPE.

MRS. F.

Time	Blood sugar	Ventricular fluid sugar
0·0	110	—
0 15	154	—
0·30	158	80
0·45	184	87
1·0	186	92
1·15	228	95
1·30	209	105
1·45	220	106
2·0	234	114

UREA EXPERIMENTS.

(Time is expressed in hours and urea in milligrams per cent. The urea meal was given immediately after the first estimation.)

MR. F.

Time	Blood urea	Lumbar fluid urea
0·0	32·4	32·4
0·15	34·1	31·9
0·30	67·6	32·1
0·45	72·4	29·8
1·0	76·2	31·0
1·15	86·6	33·0
1·30	78·2	32·8

MR. J.

0·0	30	—
0·30	35	—
1·0	36	—
1·30	42	—
1·45	58	—
2·0	61	—
2·15	54	—
2·30	53	—
2·45	56	—
3·15	61	26·0
3·30	53	26·3
3 45	50	27·0
4·0	52	24·8
4·15	48	25·0
4·30	45	25·5
4·45	52	27·5
5·0	46	27·0

MR. D.

Time	Blood urea	Lumbar fluid urea
0·0	35·6	—
0·15	41·0	—
0·30	52·4	—
0·45	62·0	—
1·0	66·4	—
1·15	69·4	—
1·30	62·0	—
1·45	62·6	—
2·0	61·6	37·7
2·15	61·4	37·4
2·30	57·6	40 6
2·45	56·4	38·8
3 0	54·6	36·5
3·15	—	38·0
3·30	52·0	37·8

Notices of Recent Publications.

Nutrition and Disease: The Interaction of Clinical and Experimental Work. By E. Mellanby: London and Edinburgh. Oliver and Boyd. 1934. Price 8s. 6d.

There is prevalent a dubiety as to the relative value of laboratory investigation and that performed at the bedside in the advancement of knowledge in medicine. The protagonists of either will do well to read this volume. Herein the author describes his personal experience gained in investigating nutritional problems, and in a lucid manner demonstrates the importance of a combination of laboratory and clinical research. Certainly the book is an able plea for more and better facilities for such combined work.

To neurologists the chapters dealing with the production of changes in the nervous system following alteration in diet are of great interest. The author demonstrates the close similarity of the experimentally produced lesions to those found in certain diseases afflicting man. The view expounded that the nervous manifestations of pellagra are closely linked to vitamin A deprivation is contrary to that usually expressed by the majority of workers on the subject. The resemblance of subacute combined degeneration of the cord to pellagra is commented upon, and the possible part played by vitamin deprivation in the former is discussed at length. Appreciating the importance of vitamins in preventing many maladies, the author suggests that the results of work in nutrition might with benefit be applied to an investigation of disseminated sclerosis. He quotes several clinical experiments of his own, but hesitates to be in any way dogmatic as to the interpretation of the results. Only work undertaken by two generations of workers will demonstrate satisfactorily the value of therapeutic measures to the disease.

The Sadleir Trust of the Royal College of Physicians is to be congratulated on making available in a form so clear and succinct the work and views of the author, a recognized leader in the study of nutrition.

The Principles and Practice of Neurology. By A. Cannon and E. T. Hayes. With a Special Clinical Examination by Professor G. H. Monrad-Krohn. London: W. Heinemann, Ltd. 1934. Price 25s.

Students of neurology seeking help in textbooks find at their disposal a number which is steadily being added to. It therefore behoves the student to discriminate with care as to which is best suited to his purpose, as often one textbook supplies some valuable information not readily available in another. In this present book, written "to present to the student and practitioner the

essentials in clinical examination, diagnosis and treatment of nervous diseases," the student will find much valuable advice and information regarding the method of clinical examination of the nervous system in the part written by Professor Monrad-Krohn. The second part, written by the authors, deals with diseases of the nervous system. Why injuries to the meninges should be included in the chapter on epidemic diseases, and hysteria in that on diseases of the spinal cord is difficult to understand. That tuberculomata are the most common spinal tumour is unlikely to receive comfirmation from neurological centres. That polycythæmia vera should receive as much space as is devoted to a description of lesions of the cauda equina and conus medullaris tends to make the book an ill-balanced one, and further, a textbook, not of neurology alone, but of diseases not usually accepted as primarily affecting the nervous system.

It is to be hoped that the authors, should they publish a second edition, will see their way to revise many of their statements and the method of presentation.

A Textbook of Medical Psychology. By E. KRETSCHMER. Translated, with Introduction, by E. B. STRAUSS. London: Humphrey Milford, Oxford University Press. 1934. Pp. 274. Price 15s.

Dr. Strauss has rendered a service to English readers in translating this well-known work, of which the German edition has been reviewed here earlier. So frequently is the Freudian or related theory assumed to be the only medical psychology, that it is of especial importance to have in this accessible form a concise presentation of the wider psychopathology which is based on a knowledge of the whole range and treatment of mental disorder as well as of psychology in its various aspects. The book is, of course, an exposition of German teaching, not always in conformity with that prevalent in England; the author's own interest and studies receive perhaps disproportionate notice. But there is no complete work in this field, and a conspectus by so active and eminent a worker as Professor Kretschmer cannot fail to be valuable. The translation is painstaking and clear.

Psychology and Psychotherapy. By WILLIAM BROWN. Third Edition. London: Edwin Arnold. 1934. Pp. 252. Price 12s. 6d.

This work might reasonably be regarded as an authoritative exposition of medical psychology in view of the author's academic position and the experience and success in therapy of which the book makes frequent mention. If this be so, it constitutes a severe criticism of the scientific claims of medical psychology. There is here no coherent theory or doctrine, but much vague speculation and appeal to superficially recorded personal experience; also expressions of conviction without evidence and unwarranted assurances that this or that is "obvious." To scientific requirements of proof less regard is paid than in comparable works in other branches of medicine and psychology. These

strictures do not apply to the short mathematical appendices which appear, however, to have hardly any connection with the rest of the book. The author's point of view is professedly synthetic as regards the differing schools of medical psychology, but actually he states what might have been thought rather advanced views twenty years ago. Of modern developments there is only superficial mention and none at all of psychopathology in the wider sense and its relations to psychiatry. The fourteen chapters of the book (which are mainly revised articles from various medical and lay journals) deal in part with clinical topics such as the psychoneuroses of war and the treatment of alcoholism, in part with the older Freudian theories, hypnotism and such philosophic problems as the mind-brain relation and the Eternal Values. The treatment of the main matter is not adequate or profound, though often adroit, smooth and even casually impressive.

Mental Defect. By LIONEL S. PENROSE. London: Sidgwick and Jackson. 1933. Pp. 183. Price 8s. 6d.

This book is published as one of a series of textbooks of Social Biology, and though by no means a textbook, it takes more account of the biological aspect of mental defect than has been the custom in earlier English works. Its main concern is the relative significance of hereditary and environmental factors in the causation of this disorder; such other material as is included is only complementary. The author is clearly better equipped to deal with these aspects of his problem than with the more clinical and pathological ones: the physical changes that may accompany defect and the psychiatric problems are skimmed over and sometimes mis-stated. The statistical treatment is better than that usually found in medical works, but shows evidence of a lack of statistical training, as in the blunder in the use of correlations on page 83. The choice of articles for footnote reference, though arbitrary, may be regarded as adequate for such a brief survey as this of the genetic and related aspects of defect. As a whole the book is interesting and does service by insisting on an essential method of study which had been neglected until the last few years.

Das Persönliche Tempo. Eine erbbiologische Untersuchung. von IDA FRISCHEISEN-KOHLER. Leipzig: Thieme. 1933. S. 63. Price M. 5.50.

Studies of constitution and inheritance now play a considerable part in psychological research. In the experiments reported in this monograph the individual tempo was measured by finding the rate at which subjects spontaneously tapped with hand or foot, or that which they found most agreable on the metronome. By these and other less measurable procedures, the authoress examined the variations in the individual himself from time to time, between him and other members of his family and between twins. The individual tempo was found to be surprisingly constant in the same subject.

The variability of tempo between uniovular twins was the same as that for a single person; for binovular twins, as for ordinary siblings, it was twice as great; hence it is concluded that hereditary influences are at least 50 per cent. responsible for the manifestation of personal tempo. The variability is still higher between persons who are not related by blood to one another. A significantly high percentage of children have the same tempo as one or both of their parents. The mode of transmission of this inherited predisposition is left in doubt. The character, however, is not so readily investigated as to its Mendelian relations as the writer assumes; there are much the same difficulties as obtain when the inheritance of intelligence is being examined. Within its limits the monograph provides useful data on constitutional attributes.

Psychiatrische Vorlesungen für Aerzte. von Kurt Schneider. Leipzig: Thieme. 1934. S. 140. Price M. 3.40.

These articles, reprinted from a German medical weekly, give a straightforward presentation of clinical psychiatry, paying particular regard to the milder or earlier forms and those symptomatic of bodily affections. The author's earlier study of psychopathic personality and related problems ensures a well-informed account, in which the actual data are presented clearly without the interpolation of needless conjectures and technical terms. It is, however, not only clear but very brief and simple and suitable rather for the medical student than for the psychiatrist.

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EDITOR.